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ARTERIOLOSCLEROSIS IN CHILDHOOD

With a Report of Two Cases

HARRIET G. GUILD, M.D., FRANK B. KINDELL, M.D. and THOMAS A. GIBSON, M.D.

From the Harriet Lane Home of the Johns Hopkins Hospital and the Departments of Pediatrics and Pathology of the Johns Hopkins University School of Medicine

Submitted for publication October 21, 1937

It is difficult to realize that, as recently as 1917 (1), not more than twenty years ago, the occurrence of hypertension in acute nephritis in children was considered sufficiently noteworthy to warrant reporting in the literature. Before that time, it was generally believed that hypertension did not occur in children and, consequently, blood pressure readings were seldom made. Since then, however, with more and more emphasis on blood pressure determinations, it has become apparent not only that hypertension is a common manifestation of nephritis in children as in adults, but that many other forms of hypertension found in the adult may be found also, even though rarely, in the child. We have recently had the opportunity to observe in detail in the Harriet Lane Home two cases of arteriolosclerosis with so-called malignant hypertension, one of which presented an unusual terminal complication, and these cases form the subject of this report.

Case 1. J. M., H. L. H. No. 92669, a white girl of 9 years 9 months, was admitted to the hospital on February 15, 1935, with the complaint of high blood pressure and kidney trouble. There was no family history of hypertension. Of importance in her past was the fact that at 7 months she had had a severe attack of acute pyelitis, with a mild recurrence at the age of 2 years, following which her tonsils had been removed. Since then she had been symptomatically so well that she had not remained under medical supervision, although she had had pertussis and varicella at 4 years, measles at 6 years, and a "Bell's palsy" of three months' duration at 8 years. During the year before admission she had developed nocturia, but, aside from that, was still considered as completely well until three months before admission when, during the course of a routine school examination, she was discovered to have a heart murmur. Further investigation then led to the discovery of a hypertension (systolic pressure, 180) and of pus and albumin in the urine. She was put to bed, still without symptoms, where she

remained for six weeks. As there was no improvement on this regime, she was sent to Florida, where her blood pressure continued to rise, reaching a systolic level above 200. Two weeks after her arrival in Florida, one month before admission to the hospital, she had a severe attack of abdominal pain and vomiting of several days' duration. This was followed by frequent less severe attacks of intermittent abdominal pain without further vomiting. Two weeks later she passed several tarry stools and, during the two weeks that ensued before admission, there was frequent gross hematuria. During this month that followed the onset of the abdominal pain, she lost ten pounds in weight, and in this condition was brought to the hospital.

Physical examination revealed a well-developed girl who was thin and rather sallow looking, but who was in no acute discomfort and was perfectly clear mentally. Her eyes moved normally and the pupils reacted to light. Hearing was acute. Some adenoid tissue and a few tonsillar remnants were present in the naso-pharynx, which was otherwise clear. Although the cardiac outlines were only slightly enlarged to percussion, the sounds were so forceful that they indicated a considerable degree of hypertrophy of the heart, and there was marked accentuation of the aortic second sound. A soft systolic murmur was partially obscured by another inconstant loud squeaking murmur of uncertain origin. The liver edge was barely palpable but no other abdominal masses were felt. There was no abdominal tenderness or rigidity. The genitalia and extremities were normal and there was no edema. Neurological examination was also negative. There was, however, marked thickening of the peripheral arteries and the blood pressure was 230/200. The fundi also showed marked changes. There was a bilateral neuro-retinitis with a subhyloid hemorrhage and partial detachment of the retina on the right. In both macular regions there were star-shaped figures, made up of hard white exudate, and the vessels everywhere showed marked narrowing and tortuosity. There was also edema of both discs, more marked on the left, with some reduction in vision.

Laboratory data: Blood examination: hemoglobin 80%; red cells 4,000,000; white cells 13,000 with normal differential; platelets normal; clotting time 3 to 4 minutes; bleeding time 1 to 2 minutes. *Urine:* albumin ++, microscopic red blood cells and pus cells, otherwise negative. *Kidney function tests: phthalein excretion*, 60% in two hours (10% in first fifteen minutes, 35% in next hour and a quarter, and 15% in the last forty-five minutes); *Mosenthal*, concentration of 1.006 to 1.014; *urea clearance*, 74% normal maximum clearance, 47% normal standard clearance. *Chemical examination of the blood:* non-protein nitrogen 33 mg. % to 50 mg. % (later); total protein 5.8 mg. % with albumin-globulin ratio of 1.55; chlorides 515 mg. %, cholesterol 400 mg. % to 220 mg. % (three days later); serum calcium 10.4 mg. % and serum phosphorus 4.2 mg. %. *Bacteriological examination:* culture of catheterized specimen of urine, B. enteritidis; throat culture, hemolytic staphylococcus; stool culture, hemolytic streptococcus, no pathogenic organisms of colon-typhoid-dysentery group; blood culture, negative. *Electrocardiogram:* normal. *Blood Wassermann:* negative.

Course: During the first week in the hospital, while the above investigations were being carried out, there was continued complaint of abdominal pain, which was often initiated by the intake of food and usually relieved by enemata. Suddenly, at the end of the week, just as preparations were being made for cystoscopic investigation, there was a severe intestinal hemorrhage, such that the hemoglobin fell from 80 to 40% and the blood pressure from 230/200 to 160/120. The blood in the stool was dull red in color and there was no pus or mucus with it. Small transfusions were given, only sufficient to prevent a further fall in hemoglobin, and with the drop in blood pressure the bleeding stopped quite abruptly. At the end of another week, blood reappeared in the stools for about two days but there was no severe hemorrhage at this time. X-rays (gastro-intestinal series and barium enema) failed to reveal any definite lesion although they gave some indication of irregularity in motility of the small intestine and hypermotility of the gastro-intestinal tract generally, suggesting ulceration. Following the X-ray studies, however, the pain practically disappeared for a period of a month and the patient ate well and gained weight, while her hemoglobin and blood pressure gradually rose again to their initial levels.

During this month of freedom from gastro-intestinal symptoms, cystoscopic investigation was carried out. Both ureters showed dilatation, with some obstruction where they passed through the bladder wall, and there was also dilatation of both kidney pelves with considerable distortion of the left one. The differential phthalein on 3/9/35 showed an appearance time of two and a half minutes on the right with an excretion of 18% in one half-hour, and an appearance time of eight minutes on the left with an excretion of 15% in one half-hour. A series of ureteral dilatations was carried out and at the end of a month the appearance time on both sides was four minutes, with 15% excretion of phthalein on each side in one half-hour. These treatments had just been completed, when, on the eighth of April, there was a sudden left-sided convulsion. Following this an ankle clonus developed, which persisted from then on, and all reflexes became and remained hyperactive. The blood pressure was 280+/190 (280 mm. Hg was as high as the manometer could register and the systolic pressure definitely exceeded this); hemoglobin 84%. Venesection accomplished only a slight fall in pressure, but, aside from occasional twitchings during the next twenty-four hours, there were no further convulsive phenomena. From then on, however, there was again frequent intermittent cramp-like abdominal pain, although, for a period of three weeks, it was not severe, there was no significant vomiting, and the abdomen remained soft and free from tenderness or other palpable abnormalities. During this period the stools also remained negative for occult blood, although the urine was frequently grossly bloody.

On the first of May, three weeks after the convulsion, the abdominal pain became more frequent and severe, the appetite failed, vomiting began, the urine became thick and purulent as well as bloody, and blood reappeared in the stools. From then on the patient became rapidly worse. Catheterization was occasionally necessary, and at times there was localized tenderness in the lower abdomen.

On the thirteenth of May the patient had a profuse diarrhoea and the following day suddenly developed symptoms of intestinal obstruction which suggested a volvulus. Surgical intervention was not attempted, in view of the hopelessness of the underlying condition, and death occurred ten days later.

From the clinical standpoint, it was clear that this girl was suffering from a chronic pyelonephritis, probably dating from the first attack of pyelitis at the age of 7 months. In view of the surprisingly good preservation of renal function, however, the degree of hypertension that she presented did not seem adequately accounted for on this basis. Furthermore, it has been our experience that, in uncomplicated cases of pyelonephritis even so advanced that the kidney function is practically reduced to zero, there is rarely more than a moderate elevation in blood pressure and often no elevation at all. It was apparent, therefore, that there must have been some other pathological condition present that involved the vascular system generally and was responsible for the extreme hypertension. It was obvious, also, that the renal disease was not primarily the cause of death but that the child died of an abdominal complication which it seemed might be related, in some way, to her hypertensive disease. There was never any positive evidence of an intussusception or polyp, and an ulcerated Meckel's diverticulum seemed unlikely, while specific intestinal infection and blood dyscrasias were definitely excluded. It was possible that multiple small ulcers in the intestinal tract (as suggested by the radiologist's interpretation of the x-ray finding of intestinal hypermotility) had bled especially freely because of the hypertension and there was no doubt as to the terminal obstruction, in whatever way it might have been related to the rest of the picture. Postmortem examination revealed a most widespread arteriolosclerosis, and extensive intestinal adhesions which were responsible for the terminal volvulus. The intestinal adhesions in turn appeared to have developed as a consequence of intestinal ulceration which was also extensive and there were widespread arteriolar lesions in the intestinal mucosa. The kidneys showed arteriolosclerotic nephritis in addition to the marked pyelonephritis. A detailed account of the positive findings at autopsy follows:

Gross Autopsy, No. 14234: The body is that of an undernourished white girl of 10 years, weighing 21 kilograms. The abdomen is not distended. There is no edema of the extremities.

Abdominal Cavity: The abdominal cavity contains 650 cc. of a yellowish cloudy fluid resembling watery fecal material from an obstructed loop of intestine. There is an extensive fibrinopurulent peritonitis.

Thoracic Cavity: Pleural and pericardial cavities are normal excepting for a thin layer of fibrin on the posterior surface of the lower lobe of the left lung.

Heart: The heart weighs 230 grams. The left ventricle is markedly thickened and hypertrophied, somewhat globular in shape and is tightly contracted. The wall measures 1.2 cm. in thickness. The right ventricle is not enlarged. There are several good-sized fatty patches in the base of the mitral valve. The coronary arteries are wide and distinctly tortuous, but there is only one coronary opening from the aorta. The large trunk runs forward from this opening and produces a normal appearing right coronary. About 2 cm. from the aorta a large branch is given off, which turns to the left and crosses the anterior part of the septum forming a normal anterior descending and left circumflex artery. The walls of the coronaries are thicker than usual and there are numerous elevated yellow plaques in the intima. Most of these are fatty but a few show a white thickening of the intima over them. There is no calcification and the vessels are wide. The ductus arteriosus is patent at the aortic end but becomes closed near the pulmonary end. There is nothing to indicate that this has been patent at any recent time.

Lungs: Both lungs are voluminous. The posterior parts of both lower lobes are reddened and on the left side there is a fibrinous exudate.

Spleen: The spleen is moderately enlarged. On section the pulp is a deep reddish-purple and is quite soft. The Malpighian bodies are distinctly visible. The splenic vein is patent and normal.

Intestines (fig. 1): The surface of the intestines shows a fibrinopurulent peritonitis and extensive adhesions. The first four or five loops of the ileum are distended, while the larger part of the terminal portion is matted together and is adherent to the pelvis on the right in the region of the ileo-cecal valve. The omentum extending downward from the transverse colon is adherent to this matted mass of ileum and is thickened. It forms a bridge under which the first two loops of ileum pass, to appear again in the upper abdominal cavity on the right. Where the distal portion of these loops passes back to the left side, the rest of the distended portion of the ileum is kinked on itself forming a definite volvulus, with a twist between 90 and 180 degrees. The loops, however, are free and the outer surfaces show only scattered patches which are deep red. There are little patches of diphtheritic exudate in the mucosa of this portion of the intestine.

Beyond this, the twisted loops which make up the rest of the ileum show tightly adherent serosal surfaces with fibrous adhesions which have been present for some time. When the loops near the ileo-cecal valve and in the pelvis are freed, another definite volvulus is found, which involves the terminal third of the ileum. These adherent loops are twisted upon themselves in a clockwise direction while the mesentery is turned through an angle of about 180 degrees with the adherent

omentum as a fixed point near the ileo-cecal valve. This portion of intestine is dark red and gangrenous, showing an extensive diphtheritic change in the mucosa when opened. There are three perforations in this area. The appendix extends medially from the cecum and is adherent in about the midline near the sacral promontory. The entire colon appears normal.

The fixed intestine, examined later, appears much less hemorrhagic and necrotic than it did when fresh, although the terminal ileum still shows extensive necrosis. In the upper portion above the volvulus there are extensive ulcerations, many of

FIG. 1. TANGLED MASS OF INTESTINE, CASE 1
The pale areas in the mucosa are the ulcers

which follow the folds in the long axis of the intestine, forming a ladder-like pattern. In other areas there are oval ulcerations with smooth margins which suggest healing. These seem old and could very well account for the adhesions. One cannot be sure whether the ulcerations were present first and led to adhesions and obstruction or whether they represent ulcerations in a chronically obstructed ileum.

Mesentery: The large mesenteric vessels are dissected out and no thrombi are found in either veins or arteries. The main mesenteric vessels and the portal vein contain no clots.

Duodenum and Stomach: Normal.

Pancreas: Normal.

Liver: The liver weighs 1000 grams and is soft. There are pale reddish islands in the center of each lobule, while the periphery is slightly but distinctly yellow. The gallbladder and bile ducts are normal.

Adrenals: The adrenals together weigh 8 grams. They are normal in size and shape. On section no lesions are found.

Kidneys (fig. 2): The left kidney weighs 45 grams; the right 80 grams. The capsules pull away with slight difficulty. Both kidneys are distorted by the presence of large depressed scars which are pale red and show only the finest roughening of the surface. The upper and lower poles are better preserved but also show

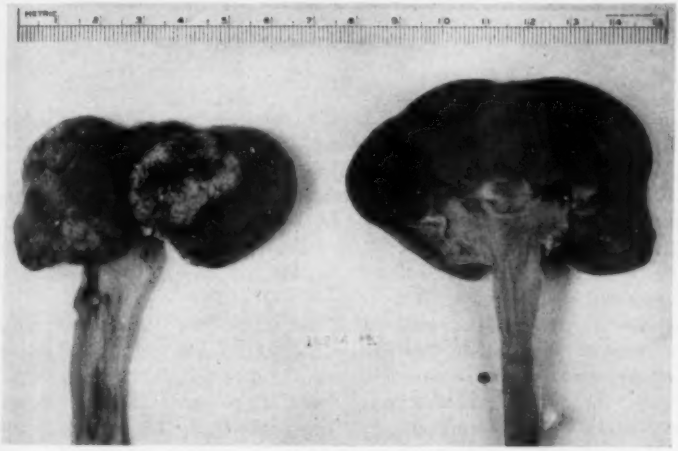

FIG. 2. KIDNEYS OF CASE 1, SHOWING LARGE SUNKEN AREAS OF SCARRING DUE TO THE PYELONEPHRITIS

small, deep scars, characteristic of a chronic pyelonephritis. The projecting masses of better preserved renal tissue are swollen and soft. Some show broad white streaks suggesting diffuse inflammatory lesions; others, a yellowish mottling. The scarring is much more extensive in the small left kidney, involving about two-thirds of its substance.

On section, wide calyces extend out into the kidneys to within 3 or 4 mm. of the surface in the areas marked by the deep scars. There are yellow streaks with reddish borders in several of the pyramids, and in the right kidney there are two distinct abscesses, one about 1 cm., the other about 1.5 cm., in diameter. Both pelves are moderately distended and their walls are thicker than usual. The lining, however, seems smooth and pale. Both ureters are also moderately distended throughout their length. The walls are thick and the linings pale with

only a few pink patches. The openings into the bladder are patent, seem slightly large and are swollen and edematous.

Bladder: The bladder is moderately distended. The submucosa is somewhat thickened but there is no acute cystitis.

Uterus, Tubes and Ovaries: These are normal.

Retroperitoneal and Thoracic Tissues: The aorta is elastic, but its wall is thick and the intima shows fairly numerous elevated fatty patches. In the abdominal aorta, there are raised white plaques which form longitudinal streaks with a curious wrinkling of the surface. The right femoral artery appears as an open tube which does not collapse, although there are no intimal changes. Other large arteries are also diffusely thickened and stand open.

Veins: The vena cava and the upper part of each iliac and femoral vein is normal.

Brain: Not examined, as its removal was not allowed.

Microscopical Notes

Heart: Except for hypertrophied muscle fibres, the heart shows no lesion.

Lungs: There is slight acute inflammation in the interstitial layers of the pleura.

Spleen: The capsule of the spleen shows a thin zone of very acute inflammation with fragmentation of the leukocytes. In the substance of the spleen the interstices of the pulp are filled with blood, while the sinuses are empty and contracted. Thickened hyalinized tiny vessels are conspicuous, particularly in the Malpighian bodies.

Pancreas (fig. 3): Throughout the section of pancreas numerous hyalinized arterioles are readily found. In these the lumen is reduced and the wall is turned into a homogeneous pink-staining material. One or two slightly larger arteries show a similar change. There is no scarring of the pancreas but there are patchy areas of atrophy. On one side, near the peritoneum, the connective tissue about the pancreas is involved in the acute inflammation.

Intestine: Sections from the inflamed portion of ileum, described in the gross, show an intense diphtheritic ileitis with some superficial ulceration. There are edema and numerous areas of hemorrhage in the submucosa and in one section taken from a site near one of the perforations the intestinal wall is necrotic. There is, however, no widespread change to suggest gangrene resulting from mechanical obstruction. It seems more probable that the whole process started as a diphtheritic and ulcerative ileitis of non-specific nature. Whether this inflammatory process developed as a consequence of the partial obstruction that was due to the adhesions or whether it was the primary cause of the adhesions and hence of the obstruction cannot be determined. There is also an acute peritonitis with mononuclear infiltration of the fatty tissue beneath the serosa. In the inflamed areas of ileum small arteries show an acute inflammation of the wall, occasionally with occlusion of the lumen by a thrombus. Some of the tiny veins also contain thrombi and one such thrombus is organized. Throughout

all the sections of ileum and also in one of the colon little hyalinized arterioles are found readily in the submucosa.

Liver: The liver cells take a faint stain and some of them are vacuolated. In the periphery of the lobule in the periportal area the cells contain a moderate amount of fat.

Adrenal (fig. 4): Little vessels in and about the capsule of the adrenal are thickened. Many of them are hypertrophied, others show fresh hyaline changes with obliteration of the cellular structure of the vessel wall. Some of these walls are much larger and thicker than usual. The adrenals themselves show no definite changes.

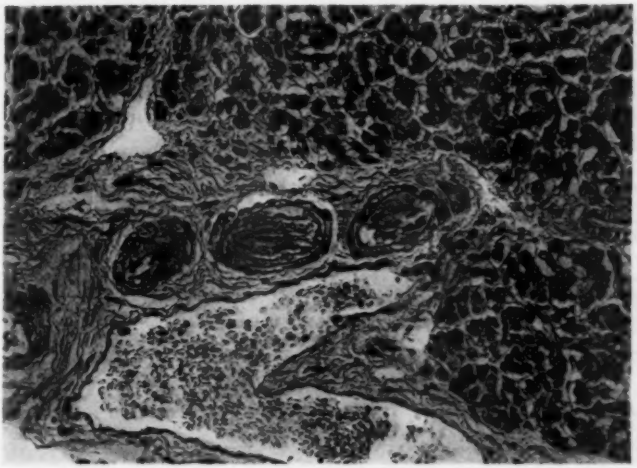

FIG. 3. SECTION OF PANCREAS FROM CASE 1, SHOWING A GROUP OF HYALINIZED ARTERIOLES

Kidneys: The sections from the shrunken left kidney show extreme destruction of the renal cortex. Evidently formerly large areas are converted into narrow zones containing only hyaline glomeruli, almost no recognizable tubules and an accumulation of round and mononuclear cells. In small areas that are better preserved there are dilated tubules, some of which contain casts. In places, epithelial cells of the tubules are loaded with colloid droplets. At one end of the section there is a rather old abscess with purulent exudate in the center surrounded by a zone of mononuclear cells. Numerous tubules contain a polymorphonuclear leukocytic exudate. The epithelial lining of the pelvis in places is thickened and shows a suggestive change from the normal transitional toward a more squamous type of cell. In other areas the epithelial lining is destroyed

and there is a leukocytic exudate on the surface. The wall of the pelvis is thickened and in many places densely infiltrated with small round cells.

In the better preserved right kidney similar changes are found. The large scars show as thinned out areas with hyaline glomeruli and destruction of tubules. There are a few small abscesses. Many dilated tubules contain a fresh purulent exudate, others contain casts. Scattered tubules show very much vacuolated epithelium while others contain colloid droplets. In the pelvis there is a chronic inflammatory reaction with old fibrous changes and numbers of mononuclear and small round cells. There is also a purulent exudate, small fragments of which lie in the pelvic lumen. Better shown in this right kidney are distinct changes in many of the glomeruli. In the scars the glomeruli are completely hyaline. Those

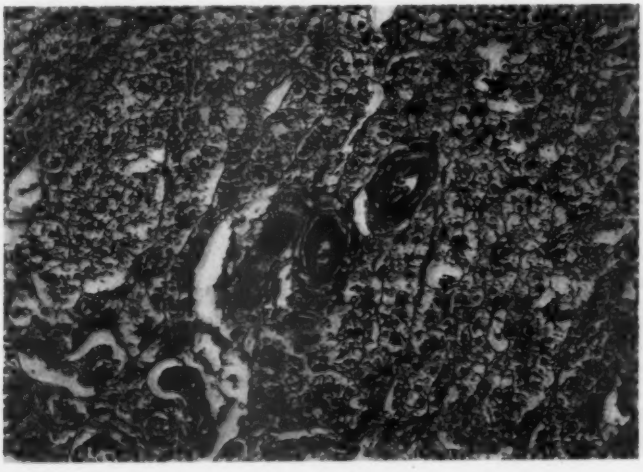

FIG. 4. SECTION OF ADRENAL FROM CASE 1, SHOWING HYALINIZED ARTERIOLES

that are not completely obliterated show interstitial changes with a thickening of the basement membrane and an interstitial fibrosis. Only an occasional isolated glomerulus shows adhesions. The intercapillary alteration is rather widespread. Many glomeruli remain normal. Numerous little thickened vessels and hyalinized arterioles are readily found (fig. 5). The alterations in the vessels of the kidney, because of the extreme change dependent upon the infection, are much less conspicuous than in the other organs. It is clear that there is a chronic pyelonephritis of long standing which has resulted from an ascending infection and upon which are superimposed more recent acute inflammatory changes. In addition to this, there is a widespread arteriolosclerosis which involves the kidneys as well as many other organs. In sections from each kidney stained for bacteria

there are both gram-positive cocci and short gram-negative bacilli in the abscesses and in the fresh exudates in the tubules.

Ureters and Bladder: Sections from both ureters show only slight changes with a few clumps of lymphocytes and little hyalinized vessels in the walls. The junction of ureter and bladder on each side is involved in a chronic inflammatory process with thickening of the submucosa of both and an infiltration with numerous round cells. There is very little fibrous thickening in either ureter or bladder. The main wall of the bladder shows less change than the trigone with only very

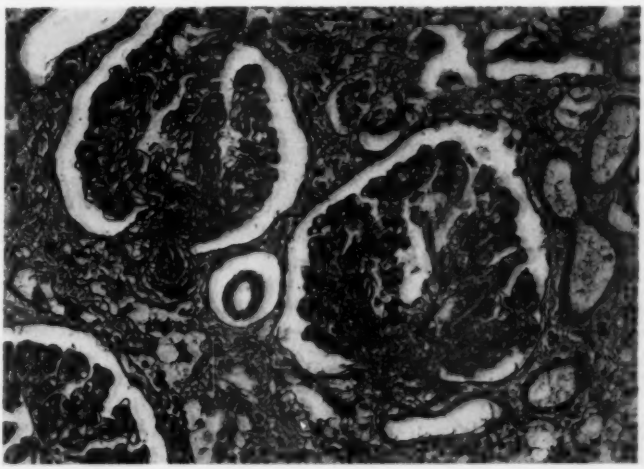

FIG. 5. SECTION OF KIDNEY FROM CASE 1, SHOWING HYALINIZED ARTERIOLE ENTERING THE GLOMERULUS AT THE LEFT AND HYALINE CHANGES IN BOTH GLOMERULI, CHARACTERISTIC OF ARTERIOLOSCLEROTIC NEPHRITIS

few round cells in the submucosa and a moderate edema, but little hyalinized vessels can be found here as elsewhere.

Ovary: There are several small follicle cysts. The peritoneal surface shows a fibrinous exudate and in one area a patch of purulent inflammatory reaction.

Oesophagus: The lower end of the oesophagus shows an intense acute inflammation with destruction of the epithelium and shallow ulceration involving the submucosa. There are patches of hemorrhage and an interstitial infiltration of the muscular wall extending even to the outermost layers. In small areas polymorphonuclear leukocytes are present, but for the most part this infiltration in the muscle is made up of mononuclear cells. Little thickened hyalinized vessels are found readily in the wall of the oesophagus.

Aorta: This shows patches of thickened intima with a few vacuolated fat-holding cells, corresponding to the small streaks of fatty infiltration.

Arteries: Sections of four medium-sized arteries show the same early intimal changes. In a few places there are foamy fat-holding cells. In other areas the intima is thickened and vacuolated.

Anatomical Diagnosis: Chronic and acute pyelonephritis; dilated ureters; chronic cystitis; generalized arteriolosclerosis; hypertrophy of left ventricle (history of hypertension); early arteriosclerosis of aorta and coronary; anomaly of coronary artery (one coronary orifice, right); adhesions of ileum and diphtheritic ileitis; volvulus; multiple perforations with fecal contents in peritoneum; fibrinopurulent peritonitis; atelectasis (slight) and fibrinous pleurisy, left lower lobe; acute oesophagitis.

As this was the first case of arteriolosclerosis that had been recognized here in a child, it was of especial interest to us when, exactly a year later, in February, 1936, another patient was referred to the Harriet Lane Home by one of the writers (T. A. G.) from Winchester, Virginia, as a case of "malignant sclerosis."

Case 2. H. J., H.L.H. No. 63795, a white girl of 9 years 10 months was admitted to the hospital on February 23, 1936, with a diagnosis of high blood pressure and convulsions. Her father, in 1934, at the age of 33, had been found to have a blood pressure of 170/90, although he was free from symptoms referable to it. The patient had had pertussis in infancy, measles and varicella a few months before the onset of symptoms. Respiratory infections had been infrequent since infancy. Otherwise the past history was uneventful save for the persistence of enuresis up to the age of 6 years and continued nocturia thereafter. The present illness began two and a half years before admission when the child started having occasional severe morning headaches, chiefly left frontal, radiating to the left side of the neck, sometimes with vomiting and usually followed by anorexia and irritability. During the next six months, these attacks gradually increased in frequency and severity until their occurrence was almost daily and they were accompanied by abdominal pain. Two weeks before she was first seen by her physician (T. A. G.) she passed bloody urine which continued intermittently bloody thereafter. The examination on March 12, 1934, revealed sluggish pupils, moderate abdominal distension with slight tenderness, many carious teeth and slight hypertrophy of the tonsils, which did not appear infected. The fundi were normal but the blood pressure was 175/130 and the radial arteries were like "pipe-stems." The urine was grossly bloody, showed albumin +++ and large clumps of pus cells. After she had spent five weeks in bed, the headaches disappeared and she felt much better, although her blood pressure continued to rise. The blood and pus disappeared from her urine, and only a trace of albumin remained. Mosenthal concentration tests on 3/26/34, 4/23/34 and 9/21/34 gave

results of 1.010 to 1.017, 1.010 to 1.014 and 1.010 to 1.020 respectively. Urea nitrogen, which was 29.9 mgm. % on 4/23/34, had fallen to 18 mgm. % on 9/21/34. The carious teeth, which gave evidence of infection, were removed. She was not seen again by her physician (T. A. G.) until December, 1935, as she had been transferred to the care of a chiropractor in the meantime and had been relatively free from symptoms. It turned out that in October, 1935, she had begun to feel badly again with anorexia, morning nausea, drowsiness and general weakness. A week later a left internal strabismus was noted and there was occasional complaint of diplopia. Abdominal pain, usually in the region of the umbilicus, often initiated by the intake of food and sometimes followed by vomiting, was frequent. In November the vomiting became more frequent and severe, abdominal pain continued, and in December there was a two-day period during which she passed large quantities of clotted blood in her stools. This was followed by several weeks of decided improvement, with gain in weight and cessation of pain until, on January 25, 1936, there were several severe generalized convulsions. Since then she had remained in bed, eating very little, because of abdominal pain, and vomiting frequently. The convulsions were also repeated a number of times and marked vascular changes were noted in the fundi. At this point the patient was referred to the Johns Hopkins Hospital for further study.

On physical examination she appeared as a well-developed girl who had obviously lost considerable weight, but who was quite comfortable and fairly alert mentally. The eyes showed a slight left internal strabismus and seemed rather prominent. Ears were normal. A few petechiae were present on the buccal mucous membranes, there were several carious teeth and small tonsils that did not appear infected. Although the cardiac outlines were not enlarged to percussion, the aortic second sound was markedly accentuated and there was a short soft systolic murmur. The spleen and liver were just palpable and the extremities were negative excepting for ecchymotic areas on the arms and legs, at the site of recent intramuscular injections of magnesium sulphate for control of the convulsions. Reflexes were active and the neurological examination was negative, aside from the slight left external rectus palsy and a slight right facial weakness. All the peripheral arteries were, however, greatly thickened, the fundi showed a marked vascular retinitis (fig. 6) and the blood pressure was 210/175.

Laboratory Data: Blood examination: hemoglobin 110%; red cells 6,000,000; white cells 20,000 with 85% polymorphs and otherwise normal differential; platelets normally abundant; clotting time 9 minutes; bleeding time 7 minutes. *Urine:* grossly bloody, albumin ++++, occasional pus cells, no casts. *Kidney function tests: phthalein excretion*, 77% in two hours (30% in first fifteen minutes, 37% in next forty-five minutes, and 10% in last hour); *variations in concentration* in single specimens (strict Mosenthal not done), 1.001 to 1.015; *urea clearance*, 64% normal maximum clearance, 71% normal standard clearance. *Chemical examination of the blood:* non-protein nitrogen 48 mg. % to 32 mg. % (later); total protein 6.2 mg. % with albumin-globulin ratio of 1.86; chlorides 506 mg. %; cholesterol 227 mg. %. *Bacteriological examination:* culture of cathe-

terized specimen of urine, B. coli; throat culture, alpha and beta hemolytic streptococci. *Electrocardiogram:* considerable variation in conduction time, at times reaching first degree block; pathological T waves. *Blood Wassermann:* negative. *X-rays: chest*, aorta diffusely dilated, cardiac shadow within normal limits, lungs clear; *sinuses*, clear; *extremities*, no evidence of calcium deposits in vessels; *stomach*, pylorus spastic. *Biopsy of gastrocnemius muscle:* definite thickening of the walls of the smaller arterioles with obliteration of the lumen in many.

Course: In the hospital the child remained weak and apathetic, eating poorly. At first she was fairly comfortable, but later was disturbed by vomiting and abdominal pain. The urine, at times grossly bloody, at other times was free from even microscopic red blood cells, and on such occasions showed only a trace of albumin, although frequently a large number of pus cells. Cystoscopic examination showed a double right ureter with, however, sterile urine from the right

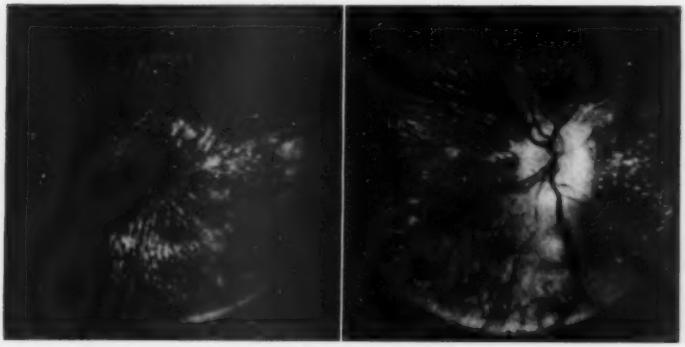

FIG. 6. PHOTOGRAPH OF FUNDI OF CASE 2, BY COURTESY OF THE WILMER CLINIC

kidney. The bladder mucosa looked normal but the bladder urine was infected with B. coli. Examination of the left kidney was never completed. A week after admission, and again a month after admission, for a period of several days, in association with the abdominal pain, the stools were tarry. Occult blood was present always. Her hemoglobin gradually fell during her stay in the hospital from 110 to 66%, but her blood pressure, excepting for a drop to 160/135 just before discharge, remained around 230/170. On two occasions there were brief convulsions, after one of which there was an increase in the right facial palsy, deviation of the tongue to the right, and temporary inability to talk. Because of the abdominal pain and tendency to vomit, she finally ceased taking food and fluids by mouth, and as it became apparent that death was imminent she was discharged by request of the parents to die at home. Death occurred from asthenia two days after discharge. A partial autopsy was performed at home by one of us (T. A. G.) and sections have been made from the material thus obtained.

The surface of both kidneys was found to be grossly reddened, the right weighing 75 grams and the left 33 grams. There was no external evidence of sclerosis and

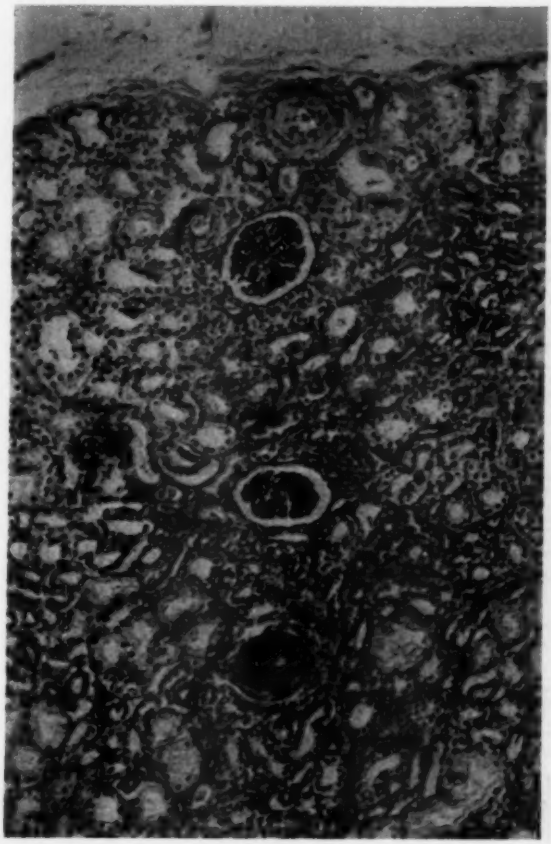

FIG. 7. SECTION OF KIDNEY FROM CASE 2, SHOWING ARTERIOLOSCLEROSIS

There is complete hyalinization of the media of the arteriole at the lower portion of the section. The arterioles with thickened media at the upper aspect represent an earlier stage of the process.

the capsules stripped easily. There was no sclerosis of the aorta and the other abdominal organs appeared grossly normal. Characteristic and marked micro-

scopic lesions of arteriolosclerosis were present in the sections of all organs available for examination, which included kidneys (fig. 7), adrenals (fig. 8), liver and spleen.

In this case, in spite of the intermittent pyuria and the presence of B. coli on culture of catheterized specimens of urine, the kidneys did not show a progressing chronic pyelonephritis, as in the other case, but an early arteriolosclerotic nephritis secondary to the vascular disease. If the larger scars seen in the microscopic sections of the small left kidney were due to a former ascending infection, this had

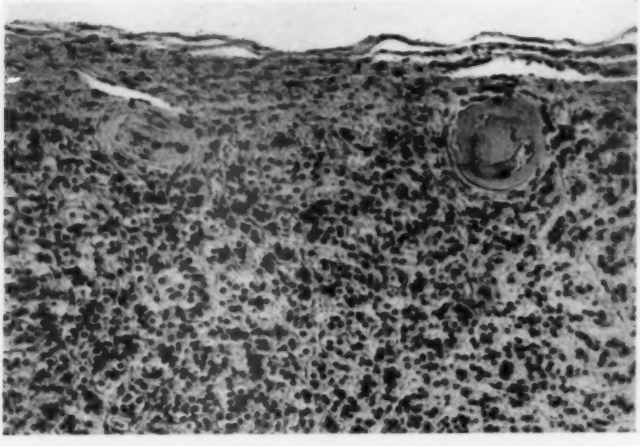

FIG. 8. SECTION OF ADRENAL FROM CASE 2, SHOWING TWO HYALINIZED ARTERIOLES WITH OBLITERATED LUMEN

healed. The pelvis of neither kidney showed any gross or microscopic evidence of pyelitis. Pathologically, then, the disease appeared here in more nearly "pure form." Since it was, however, clinically so similar to the other case in all its manifestations it offers further evidence that the symptomatology and course of the other were fundamentally referable to the vascular disease, whatever part the urinary infection may or may not have played as an etiological factor in the rôle of focus of infection. The extreme hypertension with marked vascular changes in the retina, and the varied

visceral symptoms, such as abdominal pain with frequent melena, the convulsions and hematuria, all form characteristic features of the picture of arteriolosclerosis or malignant hypertension as it is well known in the adult. Renal symptoms were no more prominent than other symptoms in either of these cases, appearing only as part of the general whole, and in both there was still good renal function up to the time of death. Although, in many cases, the renal symptoms predominate and death may result from eventual renal insufficiency, it was clear that renal insufficiency was not the cause of death in either of these, not even in the one whose kidneys showed an advanced pyelonephritis in addition to the arteriolosclerotic process. Convulsions, resulting from cerebral vascular accidents, though present in both cases and again a frequent cause of death in this disease, were likewise not the terminal event in these, although such an outcome seemed imminent. It is of interest that, in both, abdominal symptoms played a prominent part throughout. The abdominal complications were the immediate cause of death in the first case by the development of intestinal ulceration, adhesions, and obstruction, and a contributory cause in the second as a result of the patient's refusal to eat and drink because of abdominal discomfort.

A review of the literature reveals a number of undoubted instances of previously reported cases of this disease in children. In fact, in the classical account of the arteriolar changes by Gull and Sutton in 1872, there is included, among a large number of adult cases, a description of the pathological material from an 8-year old girl. In the early literature that followed, the case reports of children are few and the clinical or pathological data so meagre that it is difficult to sort out instances of this disease with any degree of assurance. The failure to make blood pressure determinations in children, the slow recognition of the part played by urinary tract infections in the production of chronic nephritis in childhood and the confusion in terminology even in the description of vascular lesions all add to the difficulty of analyzing case reports. In fact, at first, only those cases seem to have been recognized that presented prominent renal symptoms, so that the emphasis was necessarily on the renal condition, while, later, in cases such as our first one, in which a marked pyelonephritis coexisted with the arteriolosclerosis, the prominence of the

CASE	AUTHOR	SEX	AGE IN YEARS	SYMPTOMS ON FIRST EXAMINATION	BLOOD PRESSURE	HEART	FUNDI	URINE	Kid... Func...
1	Gull and Sutton (2), 1872	F	9	No clinical history given					
2	Evans (3) 1922*	F (4)	14	? (dwarfed)	240/190		Alb. retinitis	Alb. + Culture, Strep. fecalis	Sp. Gr. ... Urea (... 90, ...
3		M	14	Convulsion 7 yrs. before	195/170	Enl.	Normal		Sp. Gr. ...
				Failing vision 1 yr. Occipital headache. Occ. abd. pain	to 260/200	Enl.	Exudate & hemorrhage	Mic. Wbc and casts	Sp. Gr. ... Urea (... 67
4		M	9	Enuresis 6 mos.	190/150	Enl.	Normal	Mic. Wbc and casts	Sp. Gr. ... 1.010
				Recent headache & vomiting. Convulsions	to 215/160	Enl.	Exudate	Alb. trace Mic. occ. Wbc. and casts. Culture, neg.	Sp. Gr. ... 1.012
5		F	14	Loss of energy, fatigue 3–4 mos. Headache, abd. cramps, pains in arms. Vomiting 1 week	165/123	Enl.	Retinitis & hemorrhage	Alb. +	Sp. Gr. ... Urea (... 400
6	Schwarz (5) 1924	M	3½	Abd. pain and vomiting 4 mos. Polyuria & polydipsia	230/195		Alb. retinitis	Alb. + Mic. Rbc and Wbc	Sp. Gr. ... Urea N ... %) ...
7		F	11¼	Looked badly 6 mos. Vomiting and cramp-like abd. pain 6 wks. Polyuria & frequency	180/130 to 240/180	Enl.	Discs elevated. Some exudate	Alb. + Mic. Rbc and casts	Sp. Gr. ... Urea N ... %) ...

* In each of these four cases, Evans indicates which organs show arteriolar involvement. His description of the arteriol... the sa... typical of all the cases as a group, is, however, included in a general discussion at the end of the article. Although he uses ... points o... "diffuse hyperplastic sclerosis," he seems, from his own description and from other references made to his work in the liter... intesti...

...RSE: HEMORRHAGE, ...AIN, CONVULSIONS	DURATION AFTER DIAGNOSIS	CAUSE OF DEATH	AUTOPSY FINDINGS		
			Kidneys	Vascular lesions (small vessels)	Other
			Small. Irregular puckered surfaces, not finely granular	"Fibroid and hyaline fibroid changes in capillary arterioles"	Heart, dilated and hypertrophied
Sp. Gr. ... Urea (... 90, ...		Coma	*Right*, shrunken and coarsely granular; pelvis enlarged. *Left*, smaller; ureter dilated	Kidney, spleen, adrenal, pancreas, small and large intestine*	Heart, large. Sclerosis of large vessels
Sp. Gr. ...					
Sp. Gr. ... Urea (... 67	3 mos.	Cerebral hemorrhage	*Right*, shrunken (congenital reduction in substance). *Left*, coarsely granular	Kidney, adrenal, stomach, small and large intestine*	Heart large. Slight sclerosis of aorta, carotid and cerebral arteries
Sp. Gr. ... 1.018					
Sp. Gr. ... 1.012	6 mos.	Convulsions	Cortex thin. Ureters, hypertrophied	Kidney, spleen, adrenal, pancreas*	Heart, large. Left renal artery double. Right renal artery bifurcated. Adrenals, large
Sp. Gr. ...globin 40% Urea (... 400	? (very short)	Uremia with pericarditis	Shrunken. Coarsely granular surfaces. Pelves increased	Kidney, spleen, adrenal, pancreas*	Heart, large. Adrenals, large
Sp. Gr. ...h clotted blood in stool. Urea N ...stant severe abdominal ...%) ...in	2 mos.	Inanition and hemorrhage	No autopsy		
Sp. Gr. ...h and old clotted blood Urea N ... stools. Continuous ab- ...%) ...minal pain	2 wks.	Uremia	*Right*, 6 gm. (congenital hypoplasia). *Left*, 150 gm. ("subacute nephritis"?)	Numerous "thick-walled arteries and arterioles" in kidneys. Hyaline thickening of walls of arterioles in spleen, adrenal and in heart muscle	Heart, large. Atheromatous patches in iliac vessels. Hemorrhages in stomach with 2 ulcers; area of gangrenous intestine adherent to pelvis

...terioloses the same thing that we mean by arteriolosclerosis. He stresses the involvement of the "intimate vasculature of the organs" ...e uses the ...oints out the frequency of involvement of the intestinal vessels in these children, in contrast to the infrequency of involvement ...e literature ...intestine in the adults with whom he has had experience.

CASE	AUTHOR	SEX	AGE IN YEARS	SYMPTOMS ON FIRST EXAMINATION	BLOOD PRESSURE	HEART	FUNDI	URINE	
8	Schwarz (5) 1924	F	11½	Nocturia 6 mos. Anemia 6–8 mos. Swelling of eyes & headache 6 wks. 2 convulsions. Sl. edema of legs 1 wk.	190/140	Enl.	Swelling of discs & exudate	Alb. trace. Mic. occ. cast	Sp. (… 1.0… Incon… %. Urea … 61. P. S. … 5%.
9	Keith, Wagener & Kernohan (6), 1928	M	9	Periodic headache & projectile vomiting 5 yrs. Convulsions 5 mos. before admission	180/114 to 190/130	A_2 +++ Clin. enl. later	Retinitis & vascular changes	Alb. trace. Culture, neg.	Urea 18. P. S. … 80%.
10		F	15	Headache 4 yrs. Albuminuria 2 yrs. Left facial paralysis 2 mos.	170/115 to 200/140 to 225/145	A_2 +++	Retinitis & vascular changes	Alb. + Mic. occ. cast	Sp. (… 1.0… Urea … P. S. … 55%.
11	Kernohan, Anderson & Keith (7), 1929	F	8	Headache & vomiting 2 yrs. Nocturia. Hematuria 2 wks.	150/120 to 210/145 164/136 to 202/156	Enl.	Retinitis. Constriction and sclerosis of arteries. Edema	Grossly bloody. Alb. ++ to ++++. Mic. many Rbc. and Wbc. Culture, B. coli	Sp. (… 1.0… Urea … 36. P. S. … 70%.
	Amberg (8), 1929	F (Apparently the same case as above	8						
		M	9	Same cases as (9) and (10) above†					
		F	15						
12		F	13	Headache & vomiting 3 yrs. Epistaxis. Hematuria 4 mos. Facial weakness 6 mos.	186/100 to 218/120		Edema of discs. Constriction of arteries. Cotton wool exudate & hemorrhage	Alb. trace. Culture, neg.	
13		F	12	Headache & enuresis 2 yrs.	170/120 to 198/155		Sclerosis of arteries. Edema of discs	Alb. ++	N. P. …%. … years …/140

† These patients had not died at the time of above report. The notes relative to the course of disease and cause of death … nished by this later report and are incorporated above.

‡ These cases are included in a report of 81 cases between the ages of 9 and 64 years. Although an autopsy was not perf… of age … either of these cases, the clinical picture corresponded so closely with those in which autopsy did reveal typical widespread arte… elas… rosis, that the evidence in support of the diagnosis is wholly convincing. The authors emphasize the diffuseness of the vascu… occur… aracter…

	DURATION AFTER DIAGNOSIS	CAUSE OF DEATH	AUTOPSY FINDINGS		
			Kidneys	Vascular lesions (small vessels)	Other
...globin 20%, later 40%. ...nvulsions again 6 weeks ...er admission	6 mos.	Increasing weakness and anemia	No autopsy		
...oglobin 80%. Increas... ...headaches for 9 months	10 mos.	Convulsions	No autopsy‡		
...uria, hematuria and ...ry stools (at home)	11 mos.		No autopsy‡		
...oglobin 71%. Blood and ...umin later disappeared ...m urine	4 mos.	Died at home, cause?	No autopsy, but biopsy of the pectoral muscle during life showed arteriolar changes§		
...oglobin 79%. Devel... ...ed paresis of left orbicu... ...r muscle and unilateral ...kness. Confined to bed ...y headache	8 mos.	Still living at time of report			
...oglobin 70%. Blood ...ssure at same level for ... years, then rose to ...0/140	5 yrs.	Died, cause?	No autopsy		

...ding those of the gastro-intestinal tract and skeletal musculature) and the extreme degree of involvement of the smaller arteries ...terioles in contrast to the relative freedom of the larger ones. The article contains good photographs of the vascular lesions.

...In the article of Kernohan, Anderson, and Keith this case is included in the discussion of a group of 23 patients from 8 to 55 ...of age. There is a photograph of the section from the pectoral muscle of this patient, showing hypertrophy of the media and ...al elastic lamella of the arterioles without degenerative change. Detailed autopsy reports on two other cases, however, in which ...occurred two and four months after biopsy showed exactly the same picture as in this case, indicate the presence in the organs ...aracteristic lesions of arteriolosclerosis *with* degenerative change.

CASE	AUTHOR	SEX	AGE IN YEARS	SYMPTOMS ON FIRST EXAMINATION	BLOOD PRESSURE	HEART	FUNDI	URINE	KIDNEY FUNCTION
14	Amberg (8), 1929	M	14	Freq. headache. Fatigability 1½ yrs. (B. P. then 220/180)	164/108 to 204/158		Constriction and tortuosity of arteries	Alb. ++	Urea [illegible] 20, 19
15		F	10	Freq. headache & vomiting 1 yr. Cramps in hands & feet	170/124 to 180/130		Marked constriction of retinal arteries	Alb. +. Mic. many Wbc. Culture, B. coli	Urea [illegible] 30
16		M	9	Headache 1 yr. Occ. earache & fever. Vomiting 6 mos. Facial paralysis & convulsions	190/115 to 230/180		Choking of discs. Exudate. Hemorrhage	Alb. ++	Urea [illegible] 69, 111
17	Murphy & Gull (9), 1930	F	10	Headache, dizziness, insomnia 1 yr. Convulsions just before admission	205/155 to 130/70 to 260/150	Enl.	Narrowing of vessels. Hemorrhages	Grossly bloody at times; clear at others. Alb. 0 to +++. Mic. negative at times; many red cells and granular casts at others	Sp. Gr., 1.010; 1.020. N. P. N. %) 20. P. S. P. 45%, 2
18	Klemperer & Otani (10), 1931	M	8½	Dyspnea on exertion 1 yr. Difficulty in vision & severe headaches 3 mos. Frequent vomiting 3 wk.	235/175	A_2 +++	Extensive neuroretinitis with bilateral detachment of retina	Alb. +++. Mic. few granular casts	Sp. Gr. 1.008. Urea N. 56, 18 P. S. P. trace
19	Craig (11), 1931	F	8	Never strong. Occ. headaches with vomiting 6 yr. Severe & frequent morning headaches with vomiting, attacks of irritability, frequent epistaxis 1 yr. Convulsions 1 day	160/120 to 220/150	Sl. enl. A_2+++	"Hypertensive retinopathy" Blurring of discs, exudate, hemorrhage	Alb. +. Mic. few Wbc	Sp. Gr. 1.025; 1.022. Urea [illegible] 46, M
20	Lindsay (12), 1932	F	13	Headache, vomiting, abdominal pain, poor appetite 6 mos. Blood in urine	230/212	Enl.	"Typical albuminuric retinitis"	Alb. ++. Mic. few Rbc and granular casts	Sp. Gr. Urea N. %) 204

TAB[illegible] *Concluded*

KIDNEY FUNCTION	NURSE: HEMORRHAGE, PAIN, CONVULSIONS	DURATION AFTER DIAGNOSIS	CAUSE OF DEATH	AUTOPSY FINDINGS		
				Kidneys	Vascular lesions (small vessels)	Other
Urea (m[illegible] 20, 29	[illegible]oglobin 73%	5 yrs.	Died, cause?	No autopsy		
Urea (m[illegible] 30	[illegible]oglobin 56% and 66%	2 mos.	Died at home, cause?	No autopsy		
Urea (m[illegible] 69, 114		4 mos.	Died at home, cause?	No autopsy		
Sp. Gr. 1.018; 1.020. N. P. N. %) 29. P. S. P. 45%, 2[illegible]	[illegible]umed headache and [illegible]ssional convulsions. [illegible]quent hematuria. [illegible]ter, dyspnea and edema	1½ yrs.	Heart failure	*Right*, 75 gm. *Left*, 25 gm. Both contracted and granular	Narrowing and obliteration with medial and intimal changes in arterioles of kidneys, liver, spleen, pancreas, lungs and pectoral muscle	Heart, large
Sp. Gr. 1.008. Urea N. 56, 11[illegible] P. S. P. trace	[illegible]piness. Severe head[illegible]che, nausea and epistaxis. [illegible]ach bleeding from the [illegible]wel. Repeated convul[illegible]ons. Anemia and ap[illegible]rance of purpuric spots	3 wks.	Uremia	*Right*, 60 gm. *Left*, 40 gm. Diffuse flat granular elevations	Hyalinization of vasa afferentia in kidney and of arterioles of spleen, pancreas and adrenals. Hyaline and fatty changes also in arterioles of choroid	Heart, large. Atherosclerosis of descending aorta and coronary arteries. Acute hemorrhagic enterocolitis with ulcerative proctitis
Sp. Gr. [illegible] 1.025; 1.022. Urea (m[illegible] 46, 9[illegible]	[illegible]oglobin 90%. Repeated [illegible]acks of convulsions. [illegible]equent severe headaches [illegible]en in relatively well peri[illegible]d. Nocturia. Transient [illegible]ralysis of ext. rectus of [illegible]t eye 7 mos. after ad[illegible]ission. Increasing fun[illegible]s changes and cardiac [illegible]largement. Anginal at[illegible]ck, followed by convul[illegible]ons, 11 days before death	11 mos.	Pneumonia and heart failure following attack of convulsions	*Right*, 64 gm. *Left*, 34 gm. Arteriolosclerotic scarring of both	"Typical arteriolar changes in all organs excepting the lungs"	Heart, large. Atheroma of aorta. Medial thickening of large and medium-sized arteries
Sp. Gr. [illegible] Urea N. [illegible] %) 2[illegible] 204	[illegible]oglobin 40%. Frequent [illegible]dominal pain and vomit[illegible]g. Severe headache	4 wks.	Emaciation and dehydration	*Mic.* Glomerular tufts shrunken. Bowman's capsule thickened and fibrotic. Tubules dilated. Increased connective tissue. Lymphocytic infiltration	Thickening of vessel walls in kidney, spleen, heart. (No further description of vascular lesions, but illustrations show arteriolar changes)	

former may well have led to oversight of the latter, particularly in those cases in which there was no autopsy. It has been possible, however, to collect from the literature 20 cases in which the evidence for the existence of this condition is convincing, and these have been tabulated chronologically (table I). Other cases, that might belong, such as those of Brill and Libman (13), Baines (14), Henderson (15), and Redwood (16) have been omitted because of insufficient data. It will be noted that, in most of the earlier cases presented, the renal picture is outstanding, while among the later ones are many in which the renal picture, apart from episodes of hematuria, is relatively insignificant. This is, of course, in keeping with the greater emphasis laid in recent years upon the vascular lesions in hypertension and the better understanding of the various groups of symptoms that may appear as a manifestation of this disease according to the particular organ or organs in which the vascular changes happen to be most marked. No effort is being made in this paper to discuss the subject in detail, as it has been presented so adequately in the recent articles referred to in the bibliography, notably those of Keith, Wagener and Kernohan (6), Kernohan, Anderson and Keith (7), Murphy and Gull (9), and Klemperer and Otani (10). A brief summary of the points presented by the case reports of the children included in the table will, however, be included:

(1) The hypertension is marked, with systolic levels frequently above 200 and diastolic rarely below 150.

(2) Marked fundus changes are constant. If not present at the first examination, they appear in a relatively short period of time. When adequately described, they have been clearly of a vascular nature, with constriction of the arteries, hemorrhages, and exudate usually of the "hard white variety." Elevation of the discs is mentioned frequently and detachment of the retina, as in our case, is described once.

(3) The symptoms that occur with greatest frequency are, as might be expected, the cerebral ones, headache, vomiting and convulsions, although it is interesting that a few patients have escaped one or more of these. Cranial nerve palsies have also occurred not infrequently, usually a facial or ocular palsy. Abdominal symptoms and urinary symptoms occur with about equal frequency. Of the former, pain

and melena are striking; of the latter, enuresis or nocturia and gross hematuria. Epistaxis is quite frequent and fatigability occasionally the presenting symptom. Table II lists the order of frequency with which these various symptoms were mentioned in these cases. Cramps in the extremities were noted twice, visual disturbances twice, dyspnea and edema only once each, anginal attacks occurred once, and purpuric spots were noted once. The apparent infrequency of cardiac symptoms in children is very striking.

(4) Although the duration of the disease from the onset of symptoms to the time of death has been from three to seven years in seven of the cases, it was less than three years in the eleven others in which the duration is known, and was less than eighteen months in eight cases. That it is a "malignant" hypertension is thus clearly indicated. No form of treatment has been of any avail, although brief temporary improvement has sometimes followed long periods of rest in bed.

TABLE II

Reported symptoms in order of frequency, in the 19 cases from the literature in which the clinical history is given

Headaches	15	Melena	5
Vomiting	11	Abdominal Pain	4
Convulsions	9	Gross Hematuria	4
Enuresis or Nocturia	6	Epistaxis	4
Cranial Nerve Palsy	5	Fatigability	3

(5) The cause of death has been renal in only four of the twelve cases in which it is known. In three it has been cerebral (convulsions and hemorrhage), in three it has been due to inanition as in our second case, and in two it has been due to heart failure. Good renal function has been preserved throughout in those who did not die of uremia. We have been able to find no recorded instance in which the intestinal lesions have led to such a sequence of events as occurred in our first case, even though abdominal pain and hemorrhage from the bowel have been prominent features of the symptomatology. One of the patients described by Schwarz, however, though dying of uremia, did show at autopsy ulcers in the stomach and a gangrenous area of intestine adherent to the pelvic wall.

(6) The average age in these cases, at the time of reporting, has been 10 years, although the average age of onset in the eighteen in which the duration of symptoms is known, has been $8\frac{1}{2}$ years. In this latter group, there are six patients in whom symptoms appeared before the age of 8 years, although in only two did they appear before the age of 6. In twelve there were no symptoms before the age of 8. In general, then, it may be said that, when this condition does occur in childhood, it tends to appear in the older age group.

(7) Both sexes are affected, although in this group there is a definite preponderance of females, about 2:1 as compared with males. In larger series of all ages, recorded in the literature, the incidence is stated to be about equal in the two sexes.

(8) In a few of the cases there have been other renal lesions present in addition to the arteriolosclerotic lesions, such as infection of the urinary tract and, in two instances, a supposed congenital hypoplasia of one kidney. In three of the five in which urine cultures have been reported during life, there has been growth of bacteria from the urine. It seems probable that these other findings have been entirely coincidental, unless perchance infection in the urinary tract might be regarded as a focus of infection, liberating a toxin injurious to the arterioles throughout the body, and thus serving indirectly as a factor in the development of a widespread arteriolosclerosis.

(9) From the pathological standpoint emphasis is placed on the widespread arteriolar changes, as illustrated in the microphotographs of our cases. In all cases on which autopsies have been performed there are described, in the smaller arteries and arterioles of various organs, changes characterized by thickening of the media, frequently to the point of obliteration of the arterial lumina and, where the changes are well advanced, actual hyaline degeneration. Descriptions of other changes, secondary to the vascular ones, have not been included in the table for lack of space.

A number of practical points emerge from this analysis. Since cases of this kind are being reported with increasing frequency, now that the condition is becoming more clearly recognized, it seems that there must have been cases in the past which, due to the varied symptomatology, have escaped clinical detection. It is possible that they have hidden under the guise of unexplained convulsions, "essential"

hematuria, chronic intussusception, or myocardial failure. That any number may also have passed as chronic nephritis, without further specification, is altogether likely. With recognition of the fact that arteriolosclerosis does, however, occur in childhood and that it usually develops insidiously with considerable variation in symptoms which bring the patient under observation, according to the organ or organs predominantly affected, it seems probable that more and more cases will come to light, especially since it is now appreciated that blood pressure determinations are as essential a part of the physical examination in the child as in the adult. With such routine blood pressure determinations it is even possible that early cases may be recognized before prominent symptoms have developed and that some clues as to the etiology of the condition may thus be forthcoming.

SUMMARY

1. Two cases of extensive arteriolosclerosis in 9-year old girls are reported, with positive autopsy findings to establish the diagnosis.

2. In the first case there was a complicating chronic pyelonephritis of marked degree; in the second, in spite of the occasional appearance of pus and colon bacilli in the urine, there was no anatomically demonstrable pyelonephritis. Also, in spite of frequent periods of gross hematuria and the existence of an arteriolosclerotic nephritis, neither showed any marked impairment of renal function.

3. Abdominal symptoms, pain and melena, were prominent in both and were directly or indirectly the immediately precipitating cause of death: in the first case, through the development of intestinal ulceration, adhesions, obstruction and perforation; in the second, through interference with the intake of food and consequent inanition.

4. Cerebral symptoms were also prominent in both, but more particularly in the second case, in which they appeared as an imminent cause of death, only barely forestalled by the abdominal complication.

5. Other signs and symptoms were typical of the disease as it is well recognized in the adult. In spite of the extreme hypertension and the marked cardiac hypertrophy, however, neither child at any time showed symptoms of myocardial failure.

6. Twenty other probable cases of arteriolosclerosis in children, collected from the literature, are tabulated and the outstanding clinical features summarized. In some the evidence is based on the clinical picture only. In those on which autopsy was performed, the description of widespread thickening and hyaline changes in the media of the smaller arterioles was used as the criterion for acceptance of the diagnosis. In a few, in which the terminology was confusing, it appeared from the sum total of the evidence that this condition was meant.

7. Attention is called to the importance of regular blood pressure determinations in children, and to a consideration of the possibility of the existence of an arteriolosclerosis in explanation of a variety of presenting symptom-complexes.

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A CLINICAL STUDY OF MYOTONIC DYSTROPHY AND MYOTONIA CONGENITA WITH SPECIAL REFERENCE TO THE THERAPEUTIC EFFECT OF QUININE

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INTRODUCTION

Since the work of Santesson (28), in 1892, it has been known that quinine possesses a local action on skeletal muscle, causing fatigue with depression of contractility and irritability. However, it was not until recently that A. Wolf (36) discovered its efficacy in the treatment of myotonus. He reported 3 cases of myotonia congenita (Thomsen's disease) and 1 case of myotonia atrophica in which the inability of the muscles to relax normally was abolished by the use of quinine. Later, Kennedy and Wolf (15) reported four additional cases of myotonia atrophica favorably influenced by the drug. They also pointed out that quinine increased the muscular weakness in cases of myasthenia gravis, and that prostigmin had a similar unfavorable effect upon myotonus. Smith (30) reported three other cases of myotonia congenita in siblings confirming the value of quinine in the treatment of this disease.

The present study describes the effect of quinine, prostigmin and other drugs in eight cases of myotonia atrophica and in one of myotonia congenita. In addition the action of quinine in two cases of myasthenia gravis is discussed. In the study of four of the patients dynamograph records were made three times a day (a) during a control period, (b) during a period in which quinine alone was given, (c) during combined quinine and prostigmin therapy, and finally (d) during a further control period. These were recorded graphically upon a kymograph through a Marey tambour, the dynamometer being equipped with a suction valve. The tracings obtained provided an objective estimate of the therapeutic effect and antagonistic action of each drug.

CASE REPORTS

Case 1. H. W. (J.H.H. U 104938). This 36-year-old, white, single male was admitted to the Johns Hopkins Hospital complaining of "muscle weakness" of ten years' duration. One sister, aged 29, is reported here (Case 3), a second sister had slight muscular weakness and lost all her teeth in her twenties, while one brother, who had recently died, was said to have looked just like the patient. No evidences of the disease had been noticed in previous generations. His past health had been excellent.

The present illness was noticed first in September, 1926, when his right foot began to drag. His legs became progressively thinner and when he was lifting objects, his head would fall backwards. In 1929, for the first time, he had difficulty in relaxing his grip when grasping objects or shaking hands. His voice became deeper, frequent dental extractions were necessary and a loss of libido was noticed. Since that time there has been a gradual progression of his illness. Five years ago he could no longer rise from a supine position without help, and he was admitted to the Baltimore City Hospital. For three years he has been unable to bring food to his mouth, and he frequently falls when walking.

The *physical examination* showed that his face had a peculiar appearance produced by the hollowed temporal fossa, atrophic masseter muscles, and habitual drooping of the lower jaw (Fig. 1). A ptosis of both eyelids was apparent, the lips protruded, the lower jaw hung pendulous. There was a complete frontal baldness. The general physical examination was normal with the exception of complete maxillary and partial mandibular edentia, a high palate, a slightly enlarged thyroid, and atrophic testes. The hands became cyanotic when hanging down. The venules of the fingers and palms were found to be extremely dilated. On neurological examination the cranial nerves showed no abnormalities. The ophthalmoscopic examination was negative. He was unable to wrinkle his forehead but could close his eyes well. Pouting of the lips was impossible. The tongue dimpled when percussed. There was almost complete atrophy of the sterno-cleido-mastoids, deltoids, triceps, biceps, flexors and pronators of the forearm. The small muscles of the hand were firm and well developed and all ordinary actions could be performed, although great weakness was evident. When shaking hands firmly or grasping objects, he was unable to release his hold for several seconds. On percussing the thenar eminence the thumb became adducted and extended, holding this position for a number of seconds. His abdomen was protuberant, and there was a marked lumbar lordosis with atrophy and weakness of the erector spinalis. The vasti, peroneal and calf muscles were similarly wasted. The hamstrings, glutei, and iliopsoas muscles were strong. He walked with a steppage gait. The biceps, triceps, knee and ankle jerks could not be obtained, but the abdominal reflexes were present. No sensory loss could be demonstrated.

Examination of the blood and urine showed no abnormalities. Slit-lamp study showed a group of tiny pigment deposits on the anterior lens capsule with a few dot-like opacities. Scattered throughout the lens substance toward the posterior capsule the dot-like opacities became more numerous. The roentgenogram of

the skull showed some calcification behind the posterior clinoid and a small area of calcification in the pineal gland. In the x-rays of the chest there was irregular consolidation from the right root to the periphery along the third interspace with a similar lesion on the opposite side. The electrocardiogram was read as normal. The electrical reaction demonstrated persistent contraction in the extensors of

FIG. 1. PHOTOGRAPH, CASE 1

Note the alopecia, sunken temporal fossae, ptosis, protrusion of lips, and dependent mandible.

the forearm during the flow of the galvanic current, and an after contraction lasting after the break of faradic stimulation. A cystometric record and muscle biopsy were also performed, and will be discussed later.

From May 3 to May 14 he was given quinine sulphate, 0.6 gm. four times a day by mouth. Decrease in the myotonia was noticed after

three doses. By May 4 flexion and extension of the fingers of the left hand could be carried out rapidly (Fig. 2, B and C) and by the next day there was much less myotonus in the right hand. At the same

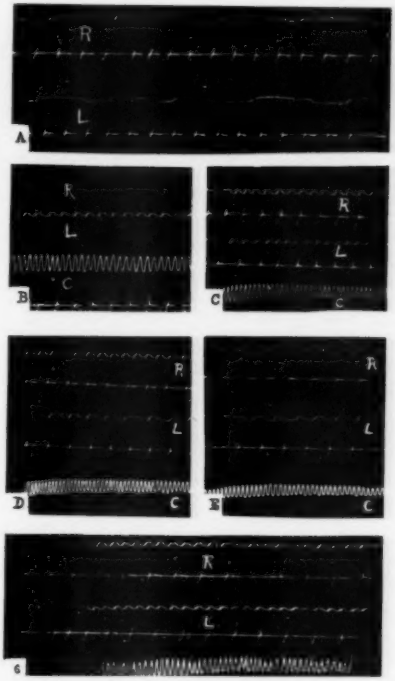

FIG. 2. DYNAMOGRAPHIC RECORD, CASE 1

The letters, R, L, and C are used, respectively, to designate right hand, left hand, and control normal in each record, and are placed beneath the respective tracing. The down strokes are those of contraction. The time recorder is set at 1.0 second. A shows hand contraction before treatment. B shows results on 5/4/37, twenty-four hours after starting 0.6 gm. quinine sulphate four times daily. The left hand is much less myotonic than the right. C recorded on 5/5/37 indicates improvement in both hands. D taken on 5/8/37, when both quinine and prostigmin were being given, shows recurrence of myotonus which is more marked in the left than the right hand. F obtained on the following day indicates myotonus of both hands while the patient was on quinine and prostigmin. No. 6 shows rapid improvement twenty-four hours after withdrawal of prostigmin.

time his legs became correspondingly less rigid. During the period of quinine medication he had moderate tinnitus but otherwise felt well. From May 6 to May 9, prostigmin, 15 mgms. four times a day by mouth, was given, in addition to the quinine. This caused a return of the myotonus, first in the left hand and then in the right hand (Fig. 2, D and E). When the prostigmin was discontinued and quinine alone administered, the original improvement returned (Fig.

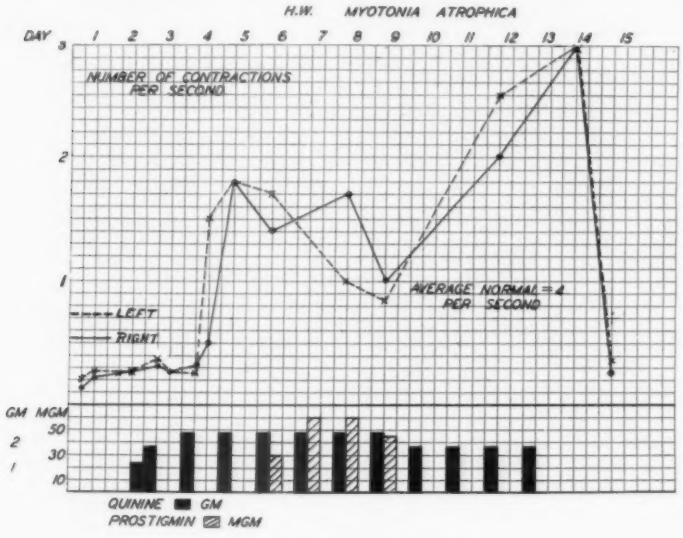

FIG. 3. CHART, CASE 1

Record of clinical course in terms of number of muscle contractions per minute in each hand related to quinine and prostigmin therapy.

3). On May 22 adrenal cortical extract (Wilson), 18 cc., was injected intramuscularly. No discernible change resulted. Throughout the periods of observation daily dynamometer readings were made; these showed that the drug failed to affect muscular strength.

Case 2. H. B. (J.H.H. 109424). This 45-year-old white male was admitted to the Baltimore City Hospital in May 1936, complaining of "weakness." His family history was interesting in that his mother, one maternal uncle, one maternal aunt and two maternal cousins had cataracts. His father was bald but healthy at

57. No one in the family had muscular weakness or myotonic symptoms, although an uncle was said to have died of the same disease. In the past his health had been good.

The present illness started at 14 after an attack of "typhoid pneumonia" when he began to fall frequently while carrying heavy objects. At 23 he had to give up his position owing to the weakness of his legs. Three years later he could move about only with the aid of a cane. Two years prior to admission he stumbled and noticed that his left foot was dragging. One year later the right foot did the same. His arms remained strong until this time, although occasionally his hands had felt "like sponges," and he had been unable to roll cigarettes. He complained of cramps in the hands but denied any real difficulty in releasing objects. Baldness first appeared at 16. One year ago his teeth were removed. He has had difficulty in swallowing and fluids regurgitate through his nose. His voice has become low and indistinct. Urinary hesitancy has been troublesome; he is sometimes incontinent when coughing.

The *physical examination* showed a short obese male, who was rather surly but coöperative. His features were unusual in the extreme frontal baldness associated with atrophy of the temporal and masseter muscles, bilateral ptosis with wasting of the orbicularis oculi, and pouting lips with weakness of the orbicularis oris. Complete edentia was present. The testes were atrophic, particularly the right. On rectal examination, the external sphincter was lax.

Neurological examination showed no cranial nerve abnormalities. There was gross wasting of the sterno-mastoids so that he was unable to lift his head from the pillow. His voice was nasal, but he swallowed without difficulty. Atrophy of the deltoids, biceps, triceps, and muscles of the forearm as well as of the vasti, peroneals and dorsi-extensors of the feet was extreme. He was unable to stand alone; the strength of the abdominal musculature and iliopsoas muscles was much reduced. The grip was maintained for five to ten seconds after the desire to relax. On percussion of the thenar eminence the thumb became adducted and extended. This position was held for several seconds. There were no sensory disturbances. The biceps, triceps, and ankle jerks were not present. The periosto-radial and knee jerks and the abdominal reflexes were barely perceptible.

The slit-lamp examination showed a normal anterior ocular segment except for the lens. A few Morgagni's corpuscles were present just beneath the capsule. Throughout the cortex, most marked near the posterior capsular region, were numerous tiny opalescent dots.

On laboratory examination the urine, stool and blood were normal. The electrocardiogram was interpreted as "normal sinus rhythm, T waves all upright and of fairly small amplitude. The only definite abnormality was a large upright T wave in the chest lead." By roentgenogram the bones of the skull were fairly thick and all the paranasal sinuses, but particularly the frontal and sphenoids, were larger than normal. The sella was normal in size and contour. The pineal gland was calcified. X-rays of the chest and heart were normal. The electrical reactions were typical of myotonus.

On May 3, he was given quinine sulphate, 0.6 gm. four times daily by mouth and this was continued until May 6. The records showed a marked reduction in myotonus which was more striking clinically than by the graphic method. At this time prostigmin, 15 mgms. orally four times a day, was ordered. There was rapid reappearance of the myotonus. The prostigmin was discontinued on May 9 and the quinine continued. The quinine was stopped on May 14 with a striking reappearance of myotonus the following day. During the period of observation no symptoms of quinine toxicity beyond tinnitus were observed. No actual improvement in strength, as read by the dynamometer, took place under this therapy.

Case 3. M. W. (U 104937). This 29-year-old unmarried white woman was admitted to the Johns Hopkins Hospital April 29, 1937, because of muscular weakness and inability to relax her grip. The family history is interesting as noted before. Her brother, aged 36 (Case 1), is suffering from the same condition. The patient was of low mentality and gave numerous versions of her illness. Her past health had evidently been good. At 18 she gave birth to a full term illegitimate child. At 23 she was again pregnant but miscarried at the fifth month. She dated her present illness to 3 years before admission when, following an attack of pneumonia, she noticed increasing weakness and inability to relax her grasp. She lost weight, had some dyspnoea and orthopnoea on exertion, and tired easily. Her jaw was weak and her forearms seemed to waste.

Physical examination showed an undernourished and poorly developed white woman. Her speech was slurred. There was moderate muscular atrophy, involving particularly the muscles of the face and neck, producing drooping expressionless features. There was slight atrophy of the fore-arms. The tongue dimpled when percussed. The thumb became adducted with a prolonged contraction when the thenar eminence was struck. There was active myotonus of the small muscles of the hands. The deep reflexes were all hyperactive. She also had complete edentia, chronic cervicitis and chronic salpingitis.

Examination of the blood and urine showed no abnormalities. An electrocardiogram showed normal sinus rhythm, left ventricular preponderance, and slight thickening of the QRS complexes in leads I and II. X-ray of the chest was essentially normal. An x-ray of the head showed some thickening of the internal table of the frontal bone and calcification in the region of the pineal gland. Ophthalmologic examination with the slit lamp showed several tiny opalescent opacities in the posterior cortex of each lens and slight clouding along the suture lines.

From May 3 to May 5 she was given quinine sulphate, 0.3 gm. three times a day by mouth. From May 6 to May 15 she received quinine

sulphate, 0.3 gm. four times daily and prostigmin, 30 to 75 mgms. daily, both orally. It was apparent to the observers, clinically and by the dynamometer records, that during the period of quinine therapy alone there was a definite decrease in the myotonus in the hands, but that when prostigmin was administered the myotonus increased in spite of the continuance of the quinine therapy.

Case 4. N. R. (J.H.H. 104741). The complaints of this patient, a white man 39 years old, admitted for study on April 13, 1937 were "cataracts," "can't let go of things" and "shortness of breath." His family history was lacking in any story of cataracts, myotonia or muscular atrophy. In the past he had had influenza at 10, and typhoid fever at 16. In 1926 he developed gonorrhoea and syphilis. At that time no evidence of a muscular disorder was noticed.

The present illness started eight years prior to admission when he noticed that his hands failed to open freely after gripping objects. In 1935 he developed dimness and cloudiness of vision and was examined in the ophthalmological dispensary when a slit-lamp study revealed "multiple semi-opaque slightly pigmented subcapsular cortical lens opacities." In 1936 he first noticed that his legs and feet were becoming weak and he was seen in the neurological dispensary where a diagnosis of myotonic dystrophy was made.

Physical examination on this admission was little different from that made in 1936, and showed a pale-complexioned man, not acutely ill and fairly coöperative. His responses were slow and querulous. There was a receding hair line most marked in the parietal region, and hollowing of the temporal fossa. Both pupils reacted rapidly to light and accommodation. Bilateral radiating lens opacities were visible with the ophthalmoscope. Complete edentia was noted. The left testis was atrophic and barely palpable, the right one was small. On neurological examination, the cranial nerves were normal. On grasping he could relax rapidly enough to release objects, but the markedly adducted and opposed position of the thumb was maintained for a number of seconds. Percussion of other muscles of the forearm and also the tongue produced a depression contracture which persisted for several seconds. Sensation was intact, and the deep and superficial reflexes were normal.

Laboratory examination showed a normal blood and urine. The blood Wassermann was negative. The electrocardiogram revealed no abnormalities. The roentgenogram of the skull showed calcification of the pineal gland. The heart and lungs were normal. A biopsy of the thenar eminence was performed.

The first record (Fig. 4A) shows the extreme myotonus while on prostigmin therapy. This was greater than that observed during the control period for which there is no comparative dynamometer record. The second tracing presents the improvement produced on

discontinuing the prostigmin and after 1.2 gms. of quinine sulphate. The last record shows further progress during quinine therapy. The drug dosages were similar to those previously mentioned.

He was discharged on 0.6 gm. of quinine sulphate twice daily. On returning to the clinic the myotonia was marked in both hands. One week later the myotonia was still present; the dose of quinine sulphate was raised to 0.6 gm. three times a day with an effective response.

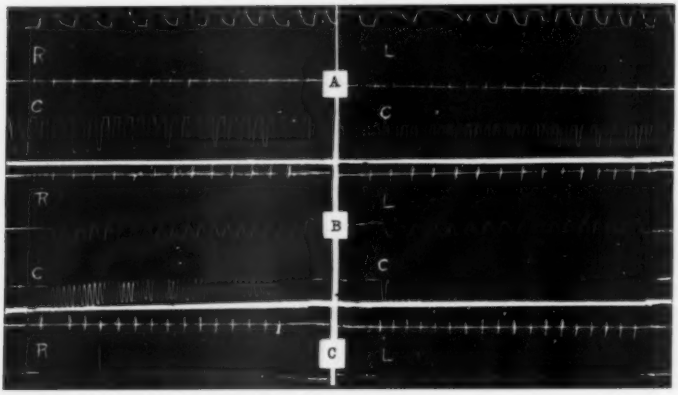

FIG. 4. DYNAMOGRAPHIC RECORD, CASE 4

The right hand tracings are on the left of the record and indicated by R. The left hand records are on the right and indicated by L. The letter C indicates normal control records. The time recorder is set at 1.0 second intervals. A shows extreme myotonus, prostigmin alone was being given. B indicates improvement twenty-four hours after discontinuance of prostigmin and the starting of quinine sulphate .6 Gm. three times daily. C shows maximum improvement four days after quinine therapy had been started.

Case 5. M. B. (J.H.H. U 107729). On May 25, 1937, this fifty-year-old white housewife was admitted to the medical ward complaining of "weakness" and "difficulty in walking." The family history was negative for muscular atrophy, myotonus or cataracts. She had had typhoid fever at 19 years of age. Twenty years prior to admission she first noticed that her back was weak. This symptom progressed, and was accompanied by a dull lumbar backache. Five years previous to this admission she was seen in the neurological dispensary when a diagnosis of myotonic dystrophy was made. She was given strychnine and ephedrine without

improvement. The lordosis and backache were improved with a body corset. In the succeeding four years her legs became less strong, and a foot-drop developed. She is now barely able to walk up stairs. She also noticed blurring of vision, deepening of her voice, and difficulty in holding her head erect. The myotonus was first noticed four years ago when she found she was unable to relax her grip.

Physical examination revealed a well developed slightly obese woman of fifty, coöperative and in no distress. The general examination was normal. Neurological study showed no cranial nerve defects. There was extreme atrophy of the sternomastoid muscles and of the temporal and masseter groups bilaterally. Weakness of the muscles of the forearm, extensors of the back, iliopsoas, vasti and the peroneal group was noticed. Her gait was waddling in character with a wide base and bilateral foot-drop. The grasp was unusual in her inability to relax for ten seconds after the act. This was more marked in the right than in the left hand. On percussing the thenar eminence the thumb became adducted and extended and held this position for approximately ten seconds before relaxing. The tongue dimpled when struck. The deep reflexes were not obtained, but the abdominal reflexes were present.

She was seen by an ophthalmological consultant who found on slit-lamp examination a spoke-shaped foggy clouding in the anterior and posterior cortex along the suture lines of both lens. Scattered throughout the cortex, but best seen anteriorly, were numerous tiny opalescent opacities.

The laboratory studies showed a normal urine and blood. The blood Wassermann reaction was negative. The electrocardiogram was interpreted as normal sinus rhythm, slight levogram, Ti and Tii upright, Tiii biphasic. The roentgenogram showed the heart moderately enlarged in all diameters. The aorta was sclerotic. The skull roentgenogram was read as normal. The electrical reactions were typically myotonic.

She was given no medication in the first three days with no change in the myotonus. From May 28 to June 4 she received parathormone intramuscularly (parathyroid ext. Lilly) in doses increasing from 5 to 9 cc. daily. At the end of this period the serum calcium had increased from 10.2 mgm. per cent to 11.4 mgm. per cent, and the phosphorus had decreased from 3.2 to 2.9 mgm. per cent without any observed clinical change in the myotonus. A 25 per cent solution of potassium chloride in doses as high as 12 cc. three times daily by mouth was administered from June 7 to June 12 without improvement. On June 24 quinine sulphate, 0.6 gm. three times daily, was started with immediate loss of myotonus. The drug was ordered for the six following days and then discontinued—with a further recurrence of muscle stiffness. Prostigmin given alone in 30 mgm. doses three

times daily definitely increased the symptoms at this time. The patient was discharged on quinine 0.3 gm. three times daily.

Case 6. R. R. (J.H.H. U 111509). This 36-year-old white, single, unemployed male was admitted to the Johns Hopkins Hospital in June, 1937, complaining of progressive weakness for the past 18 years. No one in the family had a similar ailment, and there was no history of cataracts. As a boy he was strong and active. At the age of 18 he noticed the gradual onset of generalized weakness which grew progressively worse. His arms and hands lost power. His gait changed in character so that the soles of his feet slapped on the ground when he walked. About the time of the onset of the weakness, his visual acuity began to decrease. Finally, because of cataracts, the right lens was removed 15 years and the left lens 11 years before admission. For five or six years he had had difficulty in relaxing his grip. There was no history of decreased libido or potentia, but he had never married and over the last five or six years his testicles had decreased in size.

Physical examination showed an alert coöperative male, possessing a good frame, though only 150 cm. in height, but showing obvious muscular changes. There was moderate alopecia. The speech was slurred and had a nasal twang. The eyes showed a bilateral iridectomy with operative aphakia. The facial muscles reacted sluggishly, and the masseters were wasted. There was wasting of the muscles of the forearms and arms with corresponding weakness. The extensors were weaker than the flexors. The thumb group showed the typical myotonic response to percussion. There was poor relaxation of the hands after gripping. There was loss of power in the muscles of the neck. The muscles of the feet were weak and bilateral foot-drop was present. The calf muscles were large but possessed only moderate power. They measured 35 cm. on the left and 37 cm. on the right at a level 2 cm. below the tibial tuberosity. The tendon responses were equal but sluggish in the arms. The triceps reflex was absent bilaterally. The knee jerks were hyperactive, the ankle jerks absent. There were no abnormal reflexes. No sensory changes could be made out. The testicles were definitely atrophied.

Examination of the blood, urine and stool showed no abnormalities. The blood Wassermann reaction was negative. X-rays of the chest and head were normal. The basal metabolic rate was −22. An electrocardiogram was normal. A diagnosis of myotonic dystrophy with pseudo-hypertrophy of the calf muscles was made.

He was given quinine sulphate, 0.6 gm. three times daily by mouth. After three doses of quinine, the myotonia completely disappeared, and remained absent during the week the drug was administered. There was no change in the muscular strength. Mild tinnitus was the only untoward symptom that developed. The quinine was discontinued and no medication given for four days. By the end of

this time the myotonia had returned to its original intensity. He was then given prostigmin, 30 mgm. three times a day orally. After two doses there was a marked increase in the myotonia, and this persisted during the six days this drug was taken. Again the actual muscle strength was unchanged. The patient complained bitterly about the exaggeration of his symptoms and had great difficulty with the movement of his tongue and jaw.

Case 7. L. W. (K 71079). This 43-year-old white, married, railroad watchman was seen in the dispensary of the Johns Hopkins Hospital November 21, 1935, complaining of weakness of the legs. The family history was interesting in that one brother had had bilateral cataracts removed when he was in his thirties, was partially bald, and had died of heart trouble at 46. Another brother, aged 46, wore glasses, but had no baldness or muscular weakness. A third brother aged 44, had been an invalid all his life because of muscular weakness. The patient had had small pox at 10, typhoid fever at 16, gonorrhoea at 20. Six years before examination his legs became weak, and he stumbled when walking. These symptoms increased slowly, but he could still walk fairly actively. During this time he had difficulty in opening his hands after making a fist.

Physical examination showed a tall man with large bony frame. The hair was normal in amount and texture. His voice was husky. Both testes were small and soft. He could not close the eyelids tightly. There were no cataracts on ophthalmoscopic examination. The sternomastoid muscle was almost absent on the right, and the left could just be seen. The muscles of the upper extremity were small, but showed no localized atrophy. The anterior thigh muscles were atrophied on each side. The lower legs were small, the right more so than the left. The buttocks were well developed, and the abdomen protuberant. There was generalized muscular weakness, most marked on the hands, back and feet. There was marked myotonus in the hands. Contraction of these muscles was slow but relaxation of them slower. No deep reflexes could be obtained. The abdominal reflexes were active, the cremasterics sluggish. The blood Wassermann reaction was negative. A muscle biopsy was obtained. On June 9, 1937, he was sent a prescription for quinine sulphate, 0.6 gm. four times a day by mouth. After taking the drug a week, he reported definite improvement in his grasp with diminution in the degree of myotonus.

Case 8. D. G. (B.C.H. U 23857). This 33-year-old Jewish watchmaker was admitted to the hospital complaining of a "rupture" in May, 1937. His family history was of interest for the difficulty in relaxation of muscles suffered by his half-brother and half-sister. He was operated upon one year before admission for acute appendicitis with perforation.

The muscular illness dated from 8 years of age, when he first noticed clumsiness and inability to relax his grip. At 14, he was examined with his half-brother and

half-sister by his family physician in Poland; shortly afterwards they were presented to a large clinic as cases of Thomsen's disease. The myotonia troubled him but little in his trade. He noticed aggravation of the symptom by cold and improvement on repeated exercise.

On *physical examination* he was well developed and nourished, not acutely ill. The general examination was normal with the exception of a bulge in the region of the operative scar increasing on cough or straining but easily reducible. He displayed frontal baldness and a high palate but normal genitalia. There was no evidence of cataract on ophthalmological examination. Slit-lamp study was not obtained. The cranial nerves were entirely normal. The motor system was of interest in his inability to relax his grip over periods up to 15 seconds. On percussion of the thenar eminence the thumb slowly flexed, became adducted at the metacarpo-phalangeal joint and held the position for a number of seconds before relaxing. No atrophy was present. Sensation was undisturbed and the deep and superficial reflexes were normal.

The clinical impression was myotonic dystrophy without atrophy. The diagnosis was made on the characteristic location of the myotonus, the baldness and the high palate. Thomsen's disease was considered, but the patient was not heavily muscled and the myotonus did not appear to involve the large muscle groups. The myotonus disappeared after quinine sulphate cm. 0.6 three times daily.

Case 9. H. W. (courtesy of Dr. F. R. Ford). This 30-year-old white male was referred to the hospital for treatment because of "stiff muscles." In his family history neither his mother nor father has any muscular difficulty; they had married as second cousins. His sister has some rigidity on movement, is overweight, and has been told she has "gland trouble." No one in the family has cataracts.

The present illness extended throughout the patient's childhood. He always had difficulty in relaxing his muscles, as they became "set." The stiffness was present before and after exercise but was not noticeable when he "warmed up" well. He had been able to play baseball in grammer school. He could dance, but when resting the muscles of his legs tightened and he had difficulty resuming again. The disability increased with chilling and decreased with warmth. On coughing or sneezing the abdominal muscles contracted, and he remained "doubled up" for ten or fifteen seconds. When chewing, his jaws often locked with the first few bites. Occasionally he burned his tongue because he was unable to move it rapidly enough about a hot particle of food.

On *physical examination* he was a well developed, very muscular, white male. The general examination was entirely normal. On neurological study the cranial nerves were normal. The motor system was unusual in the marked development of the musculature. The biceps, vasti, and calf muscles were large and firm on palpation. They were strong. On gripping he relaxed well, but closer examination showed he was unable to relax and immediately extend the wrist; the long

flexors were tonic and held the hand in the median position. This disappeared after several trials. On flexing the forearm on the arm and attempting sudden extension, the act was delayed, and the biceps were seen as a firm swollen mass. Percussion on the muscles of the forearm caused finger flexion, which persisted about ten seconds and then slowly died away. Dimpling could not be produced by percussion over the muscles. Sensation was undisturbed and the deep and superficial reflexes were all normal.

The electrical reactions showed after contractions with the faradic current. On galvanic stimulation with the electrode over the flexors of the forearm finger flexion persisted during the flow of the current and for 10 to 15 seconds after the break. No polar changes were noted.

The impression was Thomsen's disease. He was started on 0.2 gm. quinine sulphate three times daily, but little improvement occurred over two weeks. He noticed, however, that after coughing he no longer doubled up. The dose was then raised to 0.3 gm. three times a day with an effective response.

DISCUSSION

As the present paper deals mainly with cases of myotonic dystrophy, and the symptom complex is not well known, a brief historical and clinical outline is presented here with the contrasting features of this disease to those of myotonia congenita (Thomsen).

It is only since the individual descriptions of Batten and Gibb (2) and of Steinert (33) in 1909 that myotonic dystrophy has been clearly recognized as a separate entity unrelated to Thomsen's disease. As early as 1888 Dana (6) reported a case of myotonia with baldness, impotence, and biopsy findings typical of the disease. A series of cases was added a little later, but generally these were regarded as atypical forms of Thomsen's disease with atrophy. The independent reports of Batten and Gibb and of Steinert made it clear that the combination of myotonus usually localized in the small muscles of the hand with atrophy of the facial musculature, the sternomastoid, muscles of the forearm, vasti, and peroneal groups, formed a distinct group of cases.

The following year Greenfield (12) published his observations upon cataracts in a family of thirteen of whom five had myotonia atrophica. Two of the family showed lenticular opacities and two others presenile cataract but no myotonia. Curschmann (4) in 1912 completed the picture by stressing the significance of the frontal baldness, impotence, testicular atrophy, vasomotor changes and gradual loss of weight; dystrophic changes which had been previously observed but their

significance not realized. But it remained for Fleischer (8) in 1918 to point out that the cataracts are inherited through a series of generations before the appearance of myotonus or muscular atrophy. In the earlier generations the cataracts occur in the senile period of life, but with succeeding generations the opacities become apparent at increasingly earlier ages and finally are truly presenile. The typical cataract may be regarded as a true expression of the disease. This remarkable study of Fleischer which included some 27 families stamps the disease as heredo-familial. Macklin (19) states that it has been inherited as a Mendelian dominant in 13 families and as a recessive in 9 others.

Rouques (27) declares the disease is rare. He estimated in his all-inclusive monograph that about 200 cases are known. In America 22 cases have been reported in detail. Wolf (36) and Kennedy and Wolf (15) mention 5 others, and the present report includes eight. In this hospital 10 cases have been seen since 1928 as compared with 52 cases of muscular dystrophy and 1 case of Thomsen's disease.

The onset is usually in the late twenties or early thirties, but much younger individuals have been afflicted. Kechsner and Finesilver (16) record the case of a girl who had the first manifestations at 6 years of age. The earliest symptoms noticed by those afflicted are often weakness of the legs or hands, the former frequently appearing as a foot-drop. Backache may be the primary complaint with unsteadiness on the feet and frequent falls. Only in one of our cases (D. G.) was the rigidity of the muscles of the hands the original or main difficulty. The functional disability produced by the atrophy and muscular weakness far outweighs that of the myotonus. This is the converse of what is found in individuals suffering from Thomsen's disease who regard themselves as "muscle bound."

On examination frontal baldness, sunken temporal fossae, dependent lower jaw, ptosis, and pouting lips due to the atrophy of the facial musculature make a striking impression. Cataracts may be present, the palate is usually high and caries of the teeth is frequent. Atrophy occurs typically also in the laryngeal muscles, the sternomastoids, muscles of the forearm (particularly the brachioradialis), the peroneal and vasti groups of the leg. The abdomen is protuberant, and a lumbar lordosis is common. The testicles are small, and impotence

is the rule. The tendon reflexes cannot be obtained or are sluggish, and the gait is peculiar in its wide base combined with the steppage phenomenon.

The myotonus is best marked in the small muscles of the hand and the extensors of the forearm, but may be present in other muscle groups. When grasping objects voluntarily, the patient is unable to release his grip for several seconds. "Reactive myotonus" is the term generally applied to the dimpling and contraction of the muscles when percussed. It may be brought out in the tongue, but is usually easily obtained on striking the thenar eminence, when the thumb quickly adducts and extends, maintaining this position for a short period of time. It is generally recognized that reactive myotonia is more widespread than myotonus following voluntary movement. This may be due to the fact that active myotonus is not well brought out unless the contraction is a forcible one against some resistance. Heat is said to relieve the symptoms and cold to increase them, and the myotonic phenomenon tends to disappear if movements are repeated. However, from a series of dynamometer readings made throughout the day on our cases, no improvement was noted except possibly in the relationship of the first two or three contractions to those immediately succeeding.

The myotonic symptom appears to have its origin directly in the muscles. This is supported by the regular finding of pathological changes there and by the persistence of the symptom after novocaine nerve block, as Schaffer (29) pointed out. Kennedy and Wolf describe a more convincing experiment. Spinal anesthesia was administered to a patient with Thomsen's disease as he lay on his right side. The right lower limb became paralyzed and insensitive to pin-prick, but the myotonic phenomena remained present on percussion and electrical stimulation. It is difficult to agree with Lindsley and Curnen (18) who suggest that myotonus is neurogenic in origin owing to the persistence of electro-myographic action currents throughout the period of the after contraction.

The lenticular changes can probably be discovered in all cases with the slit lamp, but in most instances are not obvious in the clinical examination or even with an ophthalmoscope. A slit-lamp diagnosis was made in four of this series; in one (N. R.) cataracts were demon-

strated clinically, in another (R. R.) the cataracts had been removed, and in the seventh and eighth cases no clinical diagnosis was made, but the slit-lamp study was not available. The typical lesion appears as a number of colored refringent points in the posterior cortical lamella, which later may be seen as a star-shaped opacity with fine punctate opacities throughout the lens. Vögt (34) claims that these are typical, but Rivoire (25), in reviewing the problem, denies they are definitely characteristic and discusses the differential points from the cataracts of tetany, scleroderma, and Mongolian idiocy. From the standpoints of genetics a separate classification of the subcapsular cataracts suspected of being in this group seems advisable.

Characteristic electrical reactions are obtained. On the passage of a galvanic current the muscle remains contracted throughout the duration of the current. In some cases a normal twitch is observed first, but if the current is allowed to flow, a myotonic after-contracture occurs. This was observed in one of our cases and is known as the Steinert-Passler phenomenon. Various less important modifications have been published, including a depressed reaction to indirect faradic stimulation though increased to galvanic stimulation. Occasionally the anodal closing current is greater than the cathodal.

The pathological changes are regularly found in the muscles themselves. Microscopic study reveals great variation in the size of the muscle fibers, some being atrophic and others hypertrophic. There is usually an excess of sacrolemmal nuclei often invading the fibers and arranged in parallel rows along their centers. The longitudinal striations are accentuated, the transverse less well marked. Inconstant changes have been observed in the glands of internal secretion in the nine autopsies performed, but the central nervous system is usually normal. Foix and Nocolesco (10) have described cellular atrophy with pigmentation and vacuolation in the corpus striatum, pontine, dentate, and hypothalamic nuclei, but their significance is doubtful.

The course of the disease is slowly progressive and disabling. This is in contrast to that of myotonia congenita in which those afflicted may carry on some useful occupation throughout their lives. With increasing atrophy, myotonus becomes less conspicuous. The patients eventually become helpless and death intervenes before the age of

forty-five. The oldest case which has come to our notice is in a woman of fifty-nine recently seen by Dr. Frank R. Ford here. Tuberculosis is said to be the usual cause of death.

The cardinal symptoms and signs seem to occur with monotonous regularity in a large series of cases but in certain instances the differential diagnosis from Thomsen's disease, on the one hand, and muscular dystrophy, on the other, may be difficult. Rouques reviews those cases reported showing myotonus but no atrophy. Our case 8 is such an example. Curschmann (5) has described the opposing picture in his study of a family of three brothers and a cousin with the typical muscular atrophy and dystrophic symptoms but without myotonus.

The inclusion of pseudohypertrophy in the syndrome is discussed by Adie and Greenfield, who are inclined to explain the apparent hypertrophy by the contrast between the muscles free from atrophy and those contiguous which show wasting. Certainly our sixth case (R. R.) seemed to display this feature. The patient was a small man of 150 cm. in height, but his calves measured 35 and 37 cm., respectively, when measured 2 cm. below the tibial tuberosity.

It is probable that the patients with the incomplete syndrome later develop the missing atrophy, myotonus, or dystrophic phenomena. A tentative diagnosis must be considered in such instances and may be made with certainty if other members of the family are discovered to have the typical cataracts or other cardinal evidences of the disease.

Treatment and pharmacological studies. These present studies entirely corroborate the reports of Wolf, Wolf and Kennedy, and of Smith concerning the ability of quinine to abolish clinical evidence of myotonus, and that of Wolf and Kennedy concerning the opposite action of prostigmin to that of quinine in myasthenia gravis and myotonia. The graphic records show that the myotonus is often greater in one hand than in the other (figs. 2 and 3). Furthermore, with the administration of quinine improvement sometimes begins sooner in one hand than in the other.

In our patients the usual maintenance dose of quinine sulphate was 0.6 gm. three times a day by mouth. In one case this dosage abolished the myotonus entirely, but with a reduction to 0.6 gm. twice a day, the myotonus reappeared. The smallest effective dose was 0.3 gm. three times a day in a patient (case 3), who had only mild signs.

These dosages were generally larger than those previously reported when quinine hydrochloride was given by mouth.

Toxic symptoms were few. Tinnitus was invariably present, but was not of sufficient intensity to cause much discomfort. In only one instance did nausea occur, and this was on a dose of 0.6 gm. four times a day. The symptoms were promptly relieved by reducing the drug to 0.6 gm. three times a day. However, these patients have not been observed for sufficiently long periods to warrant the statement that untoward actions of quinine may not follow later.

The reduction of the myotonus by the dosages we employed by mouth usually occurred within 6 to 24 hours. In our most severe case 48 hours elapsed before improvement was apparent. Wolf and Kennedy and Smith, employing quinine dihydrochloride intravenously, reported improvement within 10 to 30 minutes. Withdrawal of the drug causes recurrence of the symptoms within a day. It should be emphasized that quinine has no effect on the muscular weakness. Daily dynamometer readings showed that muscle strength in the hands did not vary, despite the improvement in the myotonus. Whether the drug will have any influence on the wasting of the muscles in myotonia atrophica is very doubtful and can be determined only by prolonged observation. As the muscular weakness and wasting are usually the prominent complaints in myotonia atrophica the patient's benefit due to the drug is not so great as in Thomsen's disease. In three instances (cases 1, 4, 6) quinine was discontinued after the patient had received the drug regularly for four months. Thereafter, these patients complained bitterly of rigidity of the hands and pain and weakness of the legs which was now more apparent to them than before, although by graphic records little difference from the original state could be seen. It is possible that a dependence on quinine may develop, although in cases 3 and 5 with much less myotonus withdrawal was not attended by any disagreeable results.

Pharmacological studies give rise to much speculation concerning the cause of myotonus. The myotonic reaction has long been compared to the delayed relaxation of muscles poisoned by veratrine. In 1915 Hauptmann (14) and later Fünfgeld (11) pointed out the marked reaction to pilocarpine as regards pulse, sweating, tears and vomiting, but did not mention its effect on myotonus. This was not confirmed

by Adie and Greenfield (1). Kennedy and Wolf administered prostigmin, a closely related drug, to cases of myotonia and quinine to patients with myasthenia gravis. From the increase in symptoms of each disease they suggested that the drugs were mutually opposed. In our own studies the drugs were administered simultaneously Following a therapeutic effect with quinine on myotonus the addition of as little as 90 mgm. of prostigmin a day reproduced the original symptom. Two cases of myasthenia were given quinine and are briefly reported here.

Case 10. H. B. (U 107470) was a 27-year-old white male who complained of diplopia. The history and physical examination were otherwise negative except for a slight ptosis. The prostigmin test was inconclusive. He was given 1.8 gm. and 2.4 gm. of quinine on successive days and developed marked ptosis of the right eyelid, right internal strabismus and great weakness involving particularly the jaw muscles, arms, and legs. Prostigmin, 3 mgm., was given subcutaneously. Within seven minutes improvement was noted, but the effect was short-lived. It was necessary to discontinue the quinine and give regular doses of prostigmin by mouth.

Case 11. M. S. (U 107744) came to the hospital complaining of diplopia and drooping eyelids. He showed a bilateral ptosis, with limitation of extraocular movements, weakness of the palate, and of the muscles of mastication. On prostigmin daily, marked improvement took place. After ten days he was given 1.2 gm. of quinine sulphate by mouth. Within a few hours the myasthenic symptoms became pronounced with a total ptosis, inability to chew, swallow, or raise the jaw. It was necessary to give 3 mgm. of prostigmin intramuscularly. Within ten minutes he was able to lift his head and retract the eyelids to the upper corneal margin. He could close his jaws. The effect of the prostigmin was more transient than it had been before the administration of quinine.

It may be stated that when the two drugs are given simultaneously they are mutually antagonistic. Recently Harvey and Whitehill (13) have reported the use of quinine as an adjuvant to the prostigmin test in the diagnosis of myasthenia gravis. Conversely, prostigmin might be used to accentuate the myotonus in doubtful cases. The dangers of marked increase in symptoms when administering quinine in myasthenia are considerable and should be kept in mind when the drug is given as a diagnostic test or for some other therapeutic effect. Prostigmin is equally as potent when myotonus is present.

The mechanism of the action of quinine is not clearly understood.

From the pharmacological studies of Brody and Sollman (3) it is known that the reactions to indirect electrical stimuli are earlier depressed by quinine than those on direct muscle stimulation. Likewise Santesson (28) states that quinine acts after curarisation, and Starr (31) has shown that quinidine, its isomer, antagonizes the acetylcholine effect on heart muscle. It is probable that the drug exerts its influence upon both the neuromuscular junction and the muscle itself. On the other hand, physostigmin is said to delay the destruction of acetyl choline by the choline esterase of the blood stream at the neuromuscular junctions, although clinically acetyl choline, acetyl-beta-methyl choline and carbinianocholine when tried by us and others have had no effect in myasthenia gravis or on myotonus. From these few facts the mechanism of the antagonistic action of the two drugs can be hypothesized though further experimental data are necessary to confirm the present impression.

Other studies. Kennedy and Wolf consider the possibility of some related endocrine disturbance. It is well known that hyperthyroidism is often associated with myasthenia and some cases of myotonus are recorded with myxoedema. Earlier, Weiss and Kennedy (35) reported two cases showing improvement in the myotonus with the use of thyroxine. The basal metabolic determinations done in this series suggest such a relationship; two were well below normal (-18 and -22); and three others were within a normal range though two showed minus figures. Further detailed studies with thyroxine are contemplated.

The relationship of the other endocrine glands is no clearer. Faure-Beaulieu (7) in 1928 suggested the possibility of parathyroid deficiency on the basis of the cataracts not unlike those seen in tetany, the unusual myotonic contracture, the occasionally observed Chvostek or Trousseau sign and biochemical studies of lowered blood calcium or increase in the alkaline reserve. The literature of this subject was reviewed in detail by Rouques. He added normal biochemical studies on four cases of his own. Since his report three cases have been studied by Mayer and Luhan (21) and two by Lindsley and Curnen (18) in this country. None of these showed abnormalities in the blood calcium or phosphorus levels, although Lindsley and Curnen reported improvement with the intravenous injection of calcium

gluconate and calcium chloride. Our figures (Table I) likewise fail to indicate any evidence of parathyroid disease. In one instance (case 5) parathormone was given over a period of six days with a shift of the blood calcium level from 10.2 to 11.4 mgm. per cent without any noticeable improvement.

With the exception of the testicular atrophy apparent in all the males of this series suffering from myotonic dystrophy, no other direct evidence implicating any specific gland of internal secretion has been found. The x-rays of the skull showed uniformly normal sellae. The pineal gland was calcified in 4 out of 6 cases but this is not considered unusual at this age. Roentgenograms of the chest were nega-

TABLE I

Summary of biochemical studies of blood and basal metabolic rate

PATIENT	AGE	NPN	SUGAR	SERUM Cl	TOTAL PROTEIN	REFRACTIVE INDEX	SERUM Ca	SERUM P	PLASMA CO_2 COMB. POWER	BMR
		mgm. %	*mgm. %*	*m-eq./l*	*gm. %*		*mgm. %*	*mgm. %*	*vol. %*	*per cent*
Case 1	36	36	95	101	6.58	5.85	10.7	3.0	65.5	−7
Case 2	45	36	85	102		6.85	10.9	3.1	65.5	−18
Case 3	29	29		101		5.85	10.0	4.1	57.0	−3
Case 4	39	34		107				3.1	74.9	+2
Case 5	50	34	103	103.6		6.35	10.2	3.2	57.9	
Case 6	39	33	82				10.3	4.1	58.8	−22

tive for enlargement of the thymus. A trial of adrenal cortical hormone effected no improvement in one patient.

Other authors have reported favorably on the use of a multitude of agents capable of reducing myotonus. However, the reports have often been contradictory and in no instance has the drug suggested come into general use. In 1924 Weiss and Kennedy relieved myotonus with thyroxine and atropine. Kechsner and Finesilver had no favorable result from the same therapy the following year. Pamboukis (23) stated he had reduced the complaint in three cases by combining calcium chloride and acetyl-salicylic acid and in a fourth with anterior pituitary extract, while Monrad-Krohn (22) used pilocarpine effectively in a single case. In the most recent report by Kennedy and Wolf, lists of drugs effective or ineffective against myotonus and myasthenia are given. Besides quinine some improvement is said to

follow the administration of thymus, thyroid, parathyroid, viosterol and calcium. Myotonus is increased by eserine, epinephrin, belladonna and probably by veratrine and anterior pituitary. We have observed clinical improvement only with the various salts of quinine. Potassium chloride, parathormone, and adrenal cortical extract did not affect the symptom.

A study of the creatine and creatinine metabolism was carried out in 3 patients (cases 1, 5, 6) with myotonia atrophica and in 1 (case 10) with myasthenia gravis. The patients were placed on a diet low in creatine and creatinine, but providing sufficient calories and protein for metabolic requirements. Daily creatine and creatinine determinations (1) were made on the 24-hour urine specimen throughout a control period and after quinine and prostigmin had been administered. In addition, a creatine tolerance test was performed in each of the three periods. The technique employed was that described by Thorn (33). On the morning of the test 2.64 gm. of creatine (equivalent to 2.0 gm. of creatine in the urine expressed as creatinine) dissolved in 400 cc. of water were given orally. For men 80 per cent of the ingested creatine is retained normally, and for women a 70 per cent retention is normal.

One myotonic male (Case 6) showed a slight creatinuria, not affected by quinine or prostigmin. However, he retained 75–80 per cent of the ingested creatine on each occasion. Studies were not complete on the other man (Case 1) with myotonia. During a control period he showed a slight creatinuria and a definite decrease in creatine tolerance (50 per cent excretion). His creatinuria was higher during the time he was receiving quinine than during the control period. The female myotonic (Case 5) showed a normal creatinuria throughout, unaffected by the medication, and her creatine tolerance tests were likewise within a normal range. The patient with myasthenia gravis (Case 10) had a slight constant creatinuria, and normal creatine tolerance tests. The only consistent abnormality, then, was a slight creatinuria.

Certain further data were collected concerning the existence of myotonus in involuntary muscles. In no instance was a myotonic pupillary reaction obtained. The electrocardiographic studies were not consistently abnormal. In Case 2 the amplitude was diminished

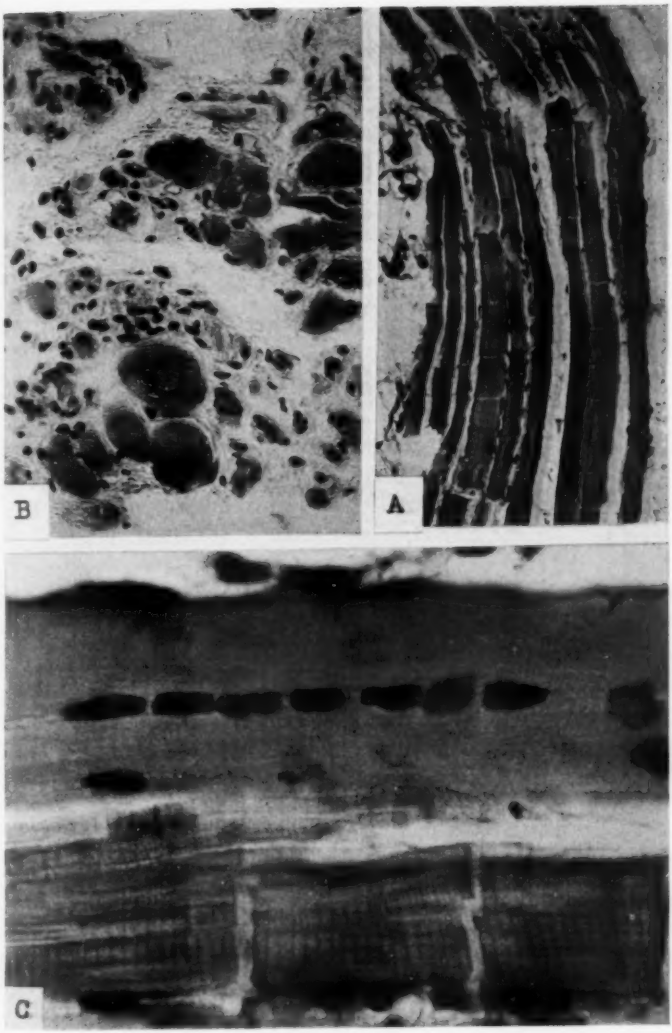

FIG. 5. PHOTOGRAPH OF BIOPSY MATERIAL, CASE 1

A: H. and E. × 150. Longitudinal section of thenar muscle, showing fatty infiltration between the fibres and increase in sarcolemmal nuclei occasionally arranged in linear rows along the center of individual fibres. B: H. and E. × 265. Transverse section of muscle bundles, with fatty infiltration, marked variation in size of individual fibres, and increase in sarcolemmal nuclei. C: H. and E. × 1000. Typical central intra-fibrillary arrangement of sarcolemmal nuclei. Note that the transverse striations are less well marked in the central fibre.

probably in keeping with the lowered basal metabolic rate (−22). In another case the QRS complex was widened. This was observed in 3 out of 4 of Rouques' cases; he suggested it as evidence of myocardial changes, although pathologically no abnormalities have ever been seen. Bradycardia and lengthened P-R intervals have been recorded by Maas and Zondek (20). In three cases (Cases 1, 2, 3) a graphic study of vesical filling was made by the method described by Langworthy (17). In two the record conformed to the normal, in the third (Case 2) symptoms of hesitancy and frequency had been elicited in the history. The graphic record showed that, although the initial pressure was within normal range, after an increment of 50 cc. of fluid had been added the resting pressure rose to 13 cc. of water. On the addition of the second 50 cc. precipitate urination occurred. Whether this is indicative of the inability of the vesical muscle to relax due to an existing rigidity it is impossible to determine. Such a reaction does explain the urinary frequency. At present, the evidence of myotonic involvement of involuntary muscle is slight.

Muscle biopsies were performed, utilizing the thenar eminence, in 5 cases (Cases 1, 2, 3, 4, 7). These specimens were examined by Dr. O. R. Langworthy (Fig. 5). In each the findings were those usually described for myotonic dystrophy. In general, there was marked atrophy of the muscle fibers with an occasional hypertrophic group of fibers. The sarcolemmal nuclei were increased in number, pyknotic and often arranged successively as cuboidal forms in long rows along the center of a single fiber. Little could be determined concerning the striations in the sections obtained, although here and there the transverse striations were not apparent. The muscle spindles appeared enlarged, with thickening of the fibrous capsule. The latter observation has not previously been made, and is now being studied further.

Note: Cases 1, 2, 3, 8 are presented here through the courtesy of Dr. Thomas R. Boggs. They were originally diagnosed at the Baltimore City Hospital and transferred to the Johns Hopkins Hospital for short periods of study. We wish to thank Dr. Frank R. Ford for permission to study case 9 and Dr. O. R. Langworthy for his kind assistance with the biopsy examinations.

SUMMARY

1. Eight cases of myotonia atrophica, and one case of myotonia congenita have been studied clinically while under treatment with quinine sulphate and various other drugs.

2. Quinine sulphate abolished the myotonus but had no effect on muscular strength.

3. Quinine sulphate counteracted the effect of prostigmin in two cases of myasthenia gravis and increased the symptoms and signs of the disease.

4. Prostigmin increased myotonus and directly antagonized the full therapeutic effect of quinine sulphate.

5. Parathyroid extract, potassium chloride, adrenal cortical extract failed to reduce myotonus.

6. A brief review of the literature is given in relation to myotonic dystrophy with a description of the disease. The clinical and laboratory data recorded in our cases are analysed in relation to previous findings and views on pathogenesis.

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HEREDITARY MALFORMATION OF THE VERTEBRAL BODIES

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Malformations of the vertebral bodies are not rare. Most frequently one sees simple variations in the number of vertebrae, such as a sixth lumbar vertebra. In other cases there may be fusion of two or more of their bodies, clefts in the midline or absence of one-half of a body, leaving a hemi-vertebra. The anomalies may be limited to a small region of the spine or less often may be extensive and widespread.

Anomalies of the cervical vertebrae produce the syndrome, described in 1912 by Klippel and Feil (1), of a short and rigid neck and a low hair-line. A variety of other symptoms may be found, particularly mirror movements, local or general paralyses, radicular pains and even ocular palsies. The lesion varies from a cervical spina bifida and simple reduction in the number of vertebrae to an irregular conglomeration of more or less fused vertebral bodies (2). Often the anomaly extends into the upper thoracic region, the lesion then being called a "cervicodorsal mass." When the thoracic malformations are more extensive, a group of serious respiratory symptoms is added to those constituting the Klippel-Feil syndrome.

Such was the case in the patients we wish to describe—a brother and sister with severe malformations of the vertebral columns. A minor anomaly of a cervical vertebra was present in their mother.

CASE REPORTS

Case 1. Female colored infant, born in 1934 after a gestation of approximately seven months. Birth weight, 2150 gm. At birth the entire spine was noted to be greatly shortened, measuring only 8 cm. in length, while the entire body was 36 cm. long. The deformities were carefully described at the age of 2 months (fig. 1). The neck was short and rigid. The head sat almost directly on the thorax; the lower ribs almost touched the iliac crests. The anterior thoracic

and abdominal walls were more nearly normal in length, so that the back was arched and the chest was convex anteriorly. The abdomen was markedly protuberant. There was scoliosis to the right in the cervico-thoracic region. No mirror-movements were noted and no palsies. Roentgenograms (fig. 2) showed extensive deformities of the entire vertebral column, most marked in the cervical and thoracic regions; numerous hemi-vertebrae were present and many of the bodies were partially fused; the ribs varied in thickness and several were fused posteriorly. The heart appeared to be shifted to the right. The infant developed rapid and difficult breathing with cyanosis, and died at the age of 6 months.

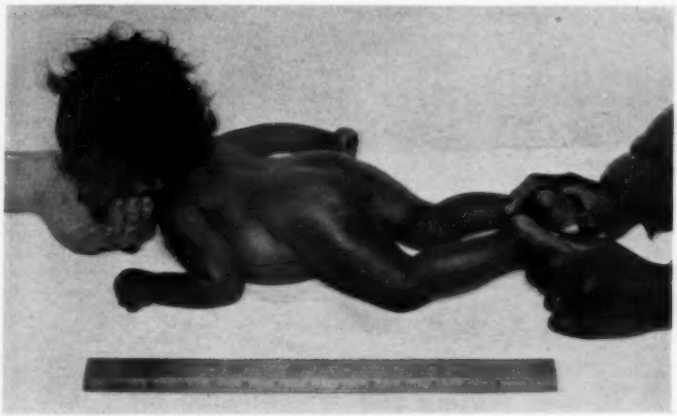

FIG. 1. Case 1. Lateral view of infant, at age of 2 months. Note the short neck, short thoracic spine, protuberant abdomen and the approximation of ilium to ribs.

Autopsy (14031): The body was poorly developed, measuring 50 cm. in length and weighing 4 kg. The head was tilted sharply to the right and backward. The neck was short and rigid. There was pronounced scoliosis of the trunk with the convexity directed to the right. The costal arch flared widely and the right costal margin was more curved than the left. The bronchial mucosa was red. Confluent areas of consolidation were present at the bases of both lungs; microscopic examination of these areas showed bronchopneumonia. The other viscera appeared normal. The heart was not displaced.

The vertebral column was removed for more careful examination, the specimen consisting of the entire spine except for the coccyx and sacrum (fig. 3). The vertebral arches were normal, as was the conformation of the foramen magnum. The removed specimen measured 13 cm. in length. The scoliosis previously described was due mainly to deformity in the thoracic and lumbar regions. Con-

siderable lordosis was also present in the thoracic region. There was a reduction in the number of vertebral bodies. In the cervical region there were only five vertebrae; in the thoracic region there were only ten. Four of these vertebrae

FIG. 2. Case 1. Roentgenogram of trunk, showing the extensive anomalies of vertebral bodies and ribs.

possessed complete bodies. The others were all defective, many being hemivertebrae; many were distorted, especially those in the mid-thoracic region. It was not clear, from a comparison of the specimen with roentgenograms of the

FIG. 3. Case 1. Roentgenogram of vertebral column from first cervical to fourth lumbar vertebra, removed at necropsy. This shows, in better detail, the malformations depicted in figure 2.

child, whether there were four or five lumbar vertebrae. Only the right half of the third lumbar body was present; the other lumbar bodies were complete. The intervertebral discs varied in thickness from 1 to 2 mm. except in the lumbar spine where they were 3 mm. thick.

The ribs were also reduced in number, there being nine on the right side and seven on the left. They varied in thickness. Some were fused near their attachments to the spine.

The spinal cord showed the usual cervical and lumbar enlargements. The conus terminalis lay opposite the first lumbar vertebra. Sections through various regions revealed normal findings. The dura mater was rather thick, and the pia-arachnoid also was perhaps slightly thickened. The spinal nerve roots presented abnormalities corresponding with the vertebral malformation. The number of roots agreed with that of the vertebrae. The roots were all paired, regardless of whether the corresponding vertebra was complete or partial. Several of the roots at first connected with one another and then separated before passing through their intervertebral foramina. The roots presented the normal differences in thickness in the various regions.

The brain appeared essentially normal. The external configuration and microscopic appearance of the cerebral hemispheres were quite normal, except possibly for an increased number of nerve cells in the subcortex. The pyramidal decussation was well formed.

Case 2. Male colored infant, of the same parentage as the infant in Case 1, born in 1933 at eight and one-half months, weighing 1875 gm. The spine was markedly shortened, measuring only 11 cm. in length. The neck was extremely short, so that the clavicles were palpable immediately below the jaws. Rigidity of the neck may be inferred from the fact that the head stayed up when the body was raised to a sitting posture. The abdomen protruded and the iliac crests almost touched the ribs. Respirations were labored. There was an apparent dextrocardia. The right testicle was undescended. Roentgenograms (fig. 4) were not clear but showed a reduction in the number of vertebrae and marked disorganization of the middle thoracic vertebrae. Fusion of many of the ribs was evident near the spine. The patient became cyanotic, respirations were rapid, and he died at the age of 19 days.

Autopsy (13129): The malformation of the spine consisted of reduction in number of the vertebrae and fusion of many of the bodies. There were six cervical vertebrae. Eleven thoracic vertebrae were present, with fusion of the second and third, fourth and fifth, and tenth and eleventh. The four lumbar vertebrae were partially fused. The sacrum was so firmly fused that individual vertebrae were hardly discernible. The second and third ribs, as well as the fourth and fifth and seventh and eighth were partially fused. The eleventh and twelfth cartilages were represented by small protuberances arising from the eleventh thoracic vertebra. The thoracic cavity was small and the lungs were atelectatic. Microscopic examination of the lungs showed widespread atelectasis with a few small patches of pneumonia. There was no dextrocardia.

The mother of these infants is a young woman who has a left accessory nipple. Roentgenograms of her entire vertebral column showed no defects in the bodies,

but the arch of the fifth cervical vertebra was defective, the right lamina being practically missing (fig. 5). The Wassermann reaction of her blood was negative.

FIG. 4. Case 2. Roentgenogram of trunk, indistinct but still showing the extensive malformations of the vertebral bodies, similar to those of case 1 (figure 2).

Cases 1 and 2 resulted from her third and second pregnancies, respectively. Her first child was born dead (in 1931) from intracranial injury during an instrumental birth; autopsy also showed atelectasis, patent foramen ovale and ductus arterio-

sus, but no vertebral abnormality was noted. The father of this child was not the father of the rest of the children. The fourth child is normal, the examina-

FIG. 5. Roentgenogram of cervical spine of mother of cases 1 and 2, showing a defect in the lamina of the fifth cervical vertebra.

tion including roentgenograms of the entire spine. The father of the infants, other than the first, is short in stature, as are other members of his family; except for a spur projecting from the left tragus, he appears normal.

DISCUSSION

The clinical features of extensive malformation of the vertebral bodies fall into two groups, depending on the location of the anomalies. The cases here described presented strikingly similar deformities and represent a combination of both syndromes:

1. Malformation of the cervical spine, the Klippel-Feil deformity. The classical signs of this lesion are the triad of shortening of the neck, limited mobility and low hair-line: the "cervical thorax." The symptoms are ordinarily not serious and do not greatly interfere with life.

2. Malformation of the thoracic spine. There is shortening of this region of the spine. This change produces thoracic lordosis, convexity of the anterior chest wall, protrusion of the abdomen and approximation of the lower ribs to the iliac crests. The size of the thoracic cavity is reduced and pulmonary expansion is restrained. Dyspnea and cyanosis ensue. The patient dies early; atelectasis and secondary infection are found at necropsy. Less extensive malformations of the thoracic vertebrae produce simple distortions of the spine, which do not have the serious import of the more extensive lesions.

The hereditary nature of malformations of the vertebral bodies is evident from their familial occurrence. The family herein described is the third family that has been reported as presenting more than one instance of the Klippel-Feil anomaly. The first was briefly mentioned by Sicard and Lermoyez (3). The mother of one of their patients who showed the typical cervical deformity, two of his brothers and a sister, all are stated to have presented the same external appearance of the neck. The second family was reviewed in greater detail by Demeler (4). Here, all the cases occurred in one generation, which consisted of four children. The oldest, a girl of 18 years, had a cervical rib, producing paresis of the right arm, and abnormal vertebral bodies in the upper cervical region; in addition she had a high palate and micrognathia. The next child, a boy of 15 years, had cervical ribs, conglomeration of the lower cervical and upper thoracic vertebrae, and occult spina bifida. The third child, a boy of 8 years, had a cervical rib, fairly severe malformations of the lower cervical and upper thoracic vertebrae, a defect in the fourth lumbar body and

elevation of one scapula. The fourth child, a boy of 6 years, showed only an absence of transverse processes of the first lumbar vertebra. Previous generations in this family had all been normal. In other families, instances of neurologic abnormalities which are frequently associated with vertebral defects have occurred in persons with normal spines. Thus the aunt and cousin of one of Bauman's (5) patients with the Klippel-Feil syndrome had mirror movements and mental defect without any noticeable deformity of the neck.

Certain genetic deductions may be made from these data. The characteristic is not sex-linked. There appear to be two factors involved in the production of the vertebral malformation. First, there is a general dysplastic tendency, as indicated by the frequent occurrence of various abnormalities in the affected individuals or their relatives, such as accessory nipple, anomalies of the heart or undescended testicle. Second, a more specific dysplastic factor is necessary for the production of vertebral anomalies as closely similar as those of cases 1 and 2 described above.

We need not go into the pathogenesis of the defect beyond agreeing with the view of inhibition or necrosis of chrondrogenic centers of the vertebrae, occurring before the eighth week of pregnancy (as judged from the menstrual history). Fusion of vertebrae would depend on inhibition of the mesenchymal condensation which leads to the formation of the intervertebral discs. It is difficult to see how, as Feil and others have maintained, cervical spina bifida and other manifestations of dysraphia can result in the production of the irregular conglomeration of vertebral bodies commonly seen in cases of the Klippel-Feil syndrome. Dysraphia may be important in some of the more orderly anomalies, such as the one recently described by Avery and Rentfro (6), in which there was partial splitting of the vertebral bodies.

A final point we wish to make is that our study of material confirms the view expressed by Streeter (7) that segmentation is not an intrinsic quality of the spinal cord but is dependent rather on the relation with the mesodermal somites, especially with the vertebrae. In case 1 in which the number of thoracic vertebrae was reduced to ten, the number of thoracic spinal nerve roots was correspondingly reduced to ten on each side. The symmetry of the roots, in this case, even where there were hemivertebrae, suggests that the partial

vertebral defects came on at a later age than the total defects of vertebrae. In other cases of hemi-vertebra, as in the one carefully studied by Brash (8), the number of spinal roots is less on the side of the defect than on the other side. The segmentation of the spinal cord, indicated by the nerve roots, depends therefore on a segmentation of the bony framework of the spine, particularly on the intervertebral foramina. An opposite view was expressed by Avery and Rentfro (6), but it must be noted that their case showed a normal number of transverse processes in spite of fusion of several vertebral bodies.

SUMMARY

This paper presents clinicopathologic reports of two cases, in one generation, of severe malformation of the bodies of cervical and thoracic vertebrae. Other anomalies were present as well in another sibling and in the mother.

The symptoms may be divided into two groups. Those dependent on the cervical deformity constitute the Klippel-Feil syndrome of short neck, limited mobility and low hair-line. As a result of the thoracic malformation the chest was short and convex anteriorly and the abdomen bulged; this produced impairment of pulmonary ventilation, fatal at an early age.

In the inheritance of the Klippel-Feil deformity there appear to be two factors: a general dysplastic factor, producing various types of anomaly; and a specific factor, producing the vertebral defect which may be almost identical in the affected members.

In one of the cases here described, a count of the spinal nerve roots demonstrated a numerical reduction corresponding with the decrease in number of the vertebrae. This demonstrates that the so-called segmentation of the spinal cord really depends upon extrinsic structures, rather than upon a fundamental pattern within the nervous system.

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A SLOWLY ABSORBED EPINEPHRIN PREPARATION

Preliminary Report

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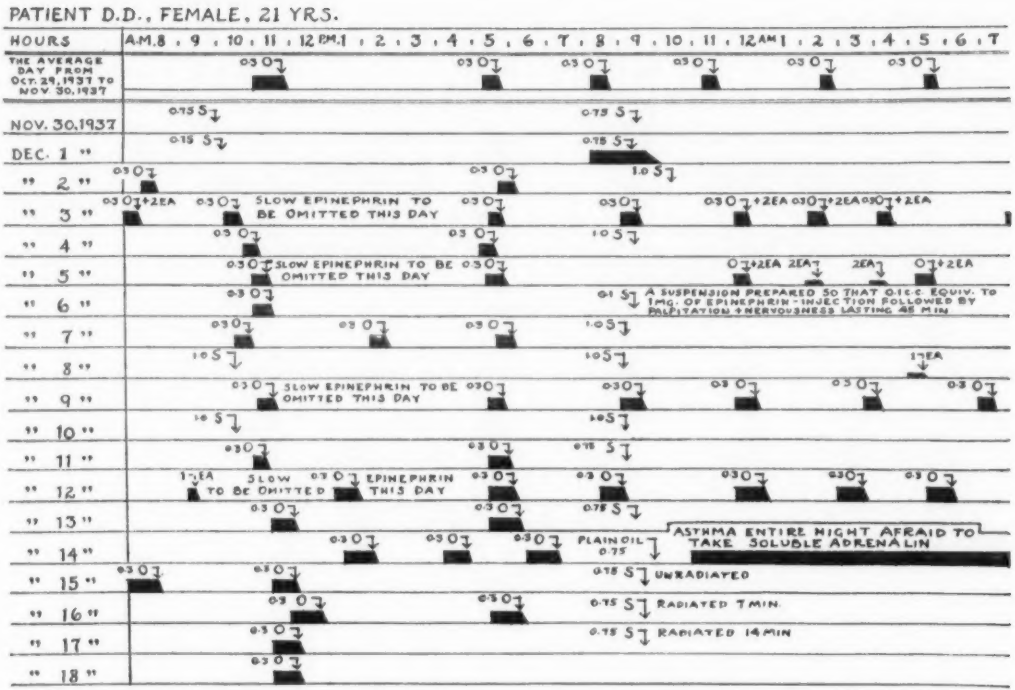
In the hope of preparing a slowly absorbed preparation of epinephrin, a suspension of powdered epinephrin base was made in purified olive oil. One cc. of the oil contained 2 mg. of epinephrin. In order to improve the suspension, vials containing the epinephrin-in-oil were exposed to supersonic radiation for 7- and 14-minute periods, respectively, and these were compared with vials that had not been exposed to supersonic influence. After a period of 24 hours, the particles of epinephrin in the unradiated vials had completely sedimented, while the radiated suspensions had partially settled out. Little difference was noted between the vials radiated for 7- and 14-minute periods. With each preparation, the particles of epinephrin were easily resuspended by shaking. Although better and more stable suspensions were made by exposure to supersonic radiation, they apparently had no greater clinical effectiveness than unradiated preparations.

The method of preparing the epinephrin used in the following experiments was comparatively simple: Purified olive oil was sterilized and placed in sterile vials. Powdered epinephrin base was weighed and added to the vials under as sterile conditions as possible. The suspension used contained 2 mg. of epinephrin base in each cc. The vials containing the epinephrin-in-oil were exposed to supersonic radiation for 7 minutes. Dry-sterilized syringes and needles were used for administration to prevent contamination with water.

In an attempt to determine whether it had a prolonged effectiveness, the "slow epinephrin," as the above preparation will be called hereafter, was administered to 5 patients suffering from chronic asthma. Four of the patients had averaged 3 to 6 injections of 0.3 to 0.5 cc. of 1–1000 epinephrin hydrochloride during the night and 2 to 4 injections during the day for a period of 3 months to 8 years. With 1 cc. to 2 cc. doses of "slow epinephrin," they remained free from asthma for 8 to 16 hours. Three of the patients were kept entirely free from symptoms for a 24-hour period by administering a morning and an evening injection of "slow epinephrin." The fifth patient had not slept a night through for 3 years because of asthma at 2:00 A.M. and again at 6:00 A.M. With 0.5 cc. of "slow epinephrin" at 9:30 P.M., he was able to sleep through the entire night without asthma.

To illustrate the prolonged effectiveness of "slow epinephrin," the management of one of the patients is shown in detail in the accompanying chart.


PATIENT D.D., FEMALE, 21 YRS.
HOURS
A.M. 8 9 10 11 12 P.M. 1 2 3 4 5 6 7 8 9 10 11 12 A.M. 1 2 3 4 5 6 7
THE AVERAGE DAY FROM Oct. 29, 1937 TO NOV. 30, 1937
NOV. 30, 1937
DEC. 1 "
" 2 "
" 3 "
" 4 "
" 5 "
" 6 "
" 7 "
" 8 "
" 9 "
" 10 "
" 11 "
" 12 "
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" 16 "
" 17 "
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SLOW EPINEPHRIN TO BE OMITTED THIS DAY
A SUSPENSION PREPARED SO THAT 0.1 C.C EQUIV. TO 1 MG. OF EPINEPHRIN - INJECTION FOLLOWED BY PALPITATION + NERVOUSNESS LASTING 45 MIN
ASTHMA ENTIRE NIGHT AFRAID TO TAKE SOLUBLE ADRENALIN
PLAIN OIL 0.75
UNRADIATED
RADIATED 7 MIN.
RADIATED 14 MIN.

Chronic bronchial asthma for the past ten years. Known to be sensitive to dust, orris root, feathers, and ragweeds. The "inked-in" areas represent attacks of asthma. The arrows marked with an O represent injections of "ordinary" epinephrin (Epinephrin-hydrochloride). The arrows marked with an S represent injections of "slow epinephrin." The arrows marked with EA represent the administration of ephedrin-amytal capsules. The dosage in each instance accompanies the arrow.

Four additional patients were treated in acute attacks of asthma. Each patient received from 0.4 cc. to 1 cc. of "slow epinephrin" and remained free from asthma from 12 to 16 hours. It was noted that the immediate response was less rapid than when solutions of epinephrin hydrochloride were used.

The first injections of epinephrin-in-oil were administered subcutaneously in the upper portion of the arm. Although no discomfort other than local tenderness for 24 to 48 hours was noted on single injections, repeated injections became definitely irritating. Consequently, the injections were made intramuscularly in the buttock and frequently repeated injections could be made without causing discomfort. No nodules developed at the site of injection in any of the patients. Peanut oil is generally considered to be less irritating than olive oil, though there is no experimental proof of this on record. Because of this accepted belief, the more recent suspensions have been prepared in purified peanut oil. Patients who have received numerous injections of epinephrin in peanut oil have experienced no discomfort whatsoever from the injections.

Additional experiments with epinephrin-in-oil are in progress but its clinical effectiveness has been so striking and its method of preparation so simple that a preliminary report seems justifiable. The method of preparation may also be applicable in the case of other hormones when it is desirable to delay absorption of injected material.

I am greatly indebted to Dr. J. A. Pierce for his assistance in the preparation of the epinephrin suspensions; to Dr. E. K. Marshall, Jr. and to Dr. A. Grollman for their suggestions; to Dr. W. T. Longcope and Dr. L. N. Gay for the use of the clinical material; to the Eli Lilly Company for the supply of powdered epinephrin base; and to Mead Johnson and Company for the use of the supersonic apparatus.

"slow epinephrin." The arrows marked with EA represent the administration of ephedrin-amytal capsules. The dosage in each instance accompanies the arrow.

BOOK REVIEWS

(These reviews represent the individual opinions of the reviewers and not necessarily those of the members of the Editorial Board of this Journal.)

The Abdominal Surgery of Children. By SIR LANCELOT BARRINGTON-WARD. 2nd ed. 333 pp. Illus. $9.00. (*Oxford University Press, New York and London, 1937.*) (*Oxford Medical Publications.*)

A sound, practical and adequately comprehensive consideration of the surgical abdominal conditions encountered in children. The first chapters, dealing with the general principles of childhood surgery, concisely summarize present day opinion. The discussions of hernia, diseases of the gallbladder, stomach, pancreas and spleen are concise re-expressions of standardized medical thought. In his chapter on the appendix the author draws upon his obviously wide personal experience. In principle this corresponds to the prevailing practice in this country, namely, immediate operation, but differs in such details as the elective use of a paramedian incision and rubber tubes for drainage. The sections on intestinal obstruction and intussusception emphasize forcefully the author's unequivocal opinion that early operation is the treatment of choice. However, he has not neglected to describe the conservative method and its results in other clinics. The chapter on errors in the development of the intestine appealed most to the reviewer; here the normalities and abnormalities are concisely described and clearly illustrated. The prognosis of Hirschsprung's disease is stated more optimistically than usual, but this opinion is supported by the author's quoted experiences. The concluding chapters deal with various abdominal neoplasms and cysts, and diseases of the female genital tract. There is also an appendix discussing anaesthesia and intravenous therapy.

The book is an excellent presentation of the subject. It is pleasantly written and adequately illustrated. Etiology and diagnosis are discussed in more detail than treatment, although the last is by no means neglected and is specific. Operative procedures are only rarely illustrated but the bibliography following each chapter is ample and modern. The reviewer believes that this volume, not intended as a book of reference for the academic pediatrician, is of particular value to the student, physician, and practicing child specialist. For the surgeon it should be supplemented by a treatise on operative technique.

R. T. S.

Surgical Treatment. By JAMES PETER WARBASSE and CALVIN MASON SMYTH, JR. 2nd ed. 2617 pp. in 3 vols., with separate index. Illus. $35.00 set. (*W. B. Saunders Company, Philadelphia and London, 1937.*)

The second edition of "Surgical Treatment" by Warbasse and Smyth is an impressive looking treatise beautifully bound in three large volumes. Upon reading these volumes, however, one is disappointed. There is a vast amount of elementary information and many unnecessary illustrations. For instance, there is no point in giving space to a picture of a bed pan. Another major criticism of the book is the paucity of references to surgical literature and the absence of a bibliography. One has the feeling that the work is simply a compilation of surgical procedures and that it was written for the general practitioner who has to brush up on his surgery preparatory to operating.

W. M. F.

Pathology. By E. B. KRUMBHAAR. (Clio Medica xix.) 206 pp. Illus. $2.00. (*Paul B. Hoeber, Inc., New York, 1937.*)

The stated purpose of each of the little books that are being published in the Clio Medica Series is to present in a readable coat-pocket edition the story of some particular phase of the history of medicine. When the subject is limited to a definitely restricted field, the treatment can be adequate in a small volume; but pathology, in the broad sense in which the term is used in the present book, is scarcely a suitable subject for such treatment, for in this sense pathology is concerned with all manifestations of disease, and its history with the changing attitude of the mind of man toward the causes, nature and significance of all morbid states. It is hardly possible to treat so vast a subject satisfactorily in 150 pocket-sized pages, or for the reader to follow such a succession of names, facts and theories from the dawn of history to the year 1936 without a slight feeling of vertigo similar to that produced by a motion picture that is being run off too swiftly.

Perhaps the most stimulating and valuable fruit of the study of the history of science is the realization that great ideas and great advances grow gradually. A too rapid presentation of the points of crystallization of great ideas fails to convey this important truth with the force that it deserves. In the present little book, for example, in treating of the development of histological pathology, which is one of the most fundamental advances ever made in scientific medicine, while it is stated that Virchow was not the first to study pathological tissues with the microscope, only one sentence is devoted to the development of histological pathology before Virchow. Especially in view of the fact that Virchow is so generally regarded as having been the first to appreciate the importance of the microscopic study of pathological tissues and as having originated the concept of histological pathology and written the first text-book on the subject, it is important for a proper understanding of the development of this fundamental advance to trace its growth through the earlier pioneer studies of Virchow's teacher, Johannes Müller, of Jacob Henle and numerous others, and to follow the rapidly growing consciousness of the importance of the histological approach to pathology as indicated by the succession of text-books such as the "Atlas der mikroskopischen pathologischen Anatomie" of Foerster, Günsberg's "Pathologische Gewebelehre",

and the 800 page "Grundzüge der pathologischen Histologie" of Wedl, in addition to the mentioned titles of the books of Vogel and Lebert, all of which preceded Virchow's "Cellularpathologie." The history of the growth of great concepts renders intelligible and in no way detracts from the epoch-making accomplishments of the masters.

Other important developments, particularly in modern times, necessarily receive only summary treatment in so brief an account. All of the important work of the past 50 years on the experimental production and study of the nature of malignant tumors is condensed in a single sentence; the entire subject of diseases caused by vitamine deficiency is likewise covered in a single sentence; neither the adrenal glands nor the sex hormones are mentioned in the brief discussion of internal secretions; and while a chapter is devoted to the theories of the causes of disease through the ages, the development of the knowledge of the relation of bacterial infection to pathology is not to be found. Nor is there any treatment of the development of the highly important biochemical side of pathological physiology.

At the end there is a chronological list of important events in the progress of pathology, on the general lines of Pagel's "Zeittafeln zur Geschichte der Medizin". It is inevitable that, unless restricted to the most epoch-making discoveries or concepts, the preparation of such a list will be governed by individual interests and will fail to satisfy all readers. In the present list, for example, the discovery of the relation of the tsetse fly to African sleeping sickness is recorded, but the discovery of the malarial parasite and of its transmission by the mosquito finds no place. That "Samuel Gross described prostatorrhoea" appears in this "List of Pathologic Milestones", but the description of hypertrophy of the prostate and its effects, by Riolan and Morgagni, is omitted. The "demonstration of the inherited rôle of the thymus in precocious growth" in 1934 is recorded, but the discovery of the relation of the pituitary to gigantism is missing.

The reviewer would insist that the above criticisms are in no sense directed at the knowledge or literary ability of the author. Dr. Krumbhaar's place as a stimulating, thoughtful, and sound writer on medical history is well known and thoroughly appreciated. This reviewer's criticism is aimed only at the crippling limitations imposed upon the author by the requirements of the edition for which the work was prepared. A more extended history of pathology from Dr. Krumbhaar's pen would assuredly be a most readable, valuable and welcome volume. However, in this day of predigested "Outlines", in which so many persons seek to be spared the mental effort that is always necessary in order to acquire a real appreciation of any worthwhile subject, there will undoubtedly be many who will feel grateful to Dr. Krumbhaar for this attempt to provide them with the high points of the history of pathology in a form that will require, as stated in the preface, only "a few hours' reading". To this group of readers the present volume can be recommended unhesitatingly. Certainly, the reviewer knows of no other brief outline of the subject that is nearly as good.

A. R. R.

Clinical Parasitology. By CHARLES FRANKLIN CRAIG and ERNEST CARROLL FAUST. 733 pp. Illus. $8.50. (*Lea & Febiger, Philadelphia, 1937.*)

This is a welcome contribution by two authors whose qualifications in writing on the subject of clinical parasitology are well recognized. The protozoa, helminths and arthropods are considered in detail. The treatment of the subject reveals the familiarity of the authors with its clinical as well as its morphologic aspects. Symptomatology, diagnosis, prognosis and treatment are adequately discussed. There are 243 well chosen engravings and a selected bibliography. The style is direct and clear.

M. M. W.

Clinical Urinalysis and its Interpretation. By ROBERT A. KILDUFFE. 428 pp. Illus. $4.00. (*F. A. Davis Company, Philadelphia, 1937.*)

The younger student will find in "Clinical Urinalysis and its Interpretation" by Robert A. Kilduffe a useful compilation of laboratory methods and descriptive matter. The text follows the usual formula for treatises on this subject, is replete with detail, and faithfully reflects the clinician's point of view. Also, as is customary in texts on this subject, the chemical tests are described in "cook book" fashion and are empirically interpreted, leaving much to be desired from the point of view of the student who has attained a foundation in chemistry and wishes to build upon it in the study of clinical medicine.

M. V. B.

Die Diffusionsanalyse am Blutplasmagel. By RUDOLF BUCHER. 123 pp. Illus. 30 Fr. Swiss. (*Benno Schwabe and Co. Verlag., Basel, 1937.*)

This is an account of a special technique for the reproducible development of *Liesegang rings* of silver chromate in suitably prepared clotted blood plasma. The character, number and time of appearance of the rings offer a basis for the examination of diffusion phenomena; and studies are reported on their correlation with age, sex and certain physiological and pathological conditions. The findings have a certain interest; but the matter as a whole seems to be another of those innumerable instances of the empirical application of partially solved physical and chemical phenomena.

B. C.

The Mechanism of Heat Loss and Temperature Regulation (Lane Medical Lectures). By EUGENE F. DU BOIS. (Stanford University Publications. University Series. Medical Sciences, vol. III, No. 4.) 95 pp. Illus. Paper bound $1.50. (*Stanford University Press, Stanford University, California, 1937.*)

"The Mechanism of Heat Loss and Temperature Regulation" summarizes the extensive studies of the Russell Sage Institute which cover a period of many years. The titles of the five lectures describe adequately the material covered: I. Heat Production and Heat Loss; II. Radiation, Convection and Vaporization; III. The Significance of the Surface Area of the Body; IV. Regulation of Body

Temperature; V. Chills and Fever. The subjects are dealt with primarily from the viewpoint of the physiologist, although the background of observation comes from the hospital wards, animal experiments and the physics laboratory. The lectures have condensed a wealth of material in a way to make it available to the average physician, and have presented a broad outlook on this aspect of physiology which makes the volume not only a source of information but also points the way to a better understanding of disease.

E. M. B.

Clinical Allergy. By LOUIS TUFT. 711 pp. Illus. $8.00. (*W. B. Saunders Co., Philadelphia and London, 1937.*)

A definite need for a textbook on Allergy stressing clinical manifestations, and written in simple language so as to be readily comprehensible to the general physician and the medical student, prompted the author to compile this text This he has succeeded admirably in doing, and the confusing terminology beclouding this field has been greatly simplified. Following a discussion of anaphylaxis and allergy, including the general principles of diagnosis and treatment, basic aetiologic types—drug, food, pollen, bacterial and physical allergies—are presented; thereafter follow the clinical types—hay fever, perennial allergic rhinitis, gastro-intestinal allergy and migraine. A special section is devoted to skin manifestations, including urticaria, angioneurotic oedema and eczema. A special chapter is also devoted to allergy in childhood, and to the relationship between allergy and other specialties. A useful appendix covers briefly investigative methods, special diets and recipes, and sources of common allergens. In addition to the clarity of presentation, the author has tried to present the various views and the majority opinion on conflicting subjects, of which there are so many in this field. Certain conclusions of the author based on collective opinion cited are, however, open to objection. For example, reagins in pollen hay fever are not regularly altered by treatment, but the author leaves the impression repeatedly that an increase occurs; again, the conclusion that sinus infections are the result of rather than the cause (in part) of asthma is surprising. In children sinus infection may be coincident with, or a complication of, the allergic reaction, but in adults such infections are considered a frequent, if not the most frequent, cause of bronchial asthma. The Prausnitz-Kustner passive transfer procedure receives little consideration as a method of clinical study; whereas, for the reviewer and for many other physicians, it is a very important means of diagnosis in cases of eczema, urticaria, in patients with highly reactive skins and in infants it may be the only means of determining existing hypersensitivity. Notwithstanding these discrepancies, this book is probably the best available for students and the general physician for whom it has been written.

W. L. W.